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Total synthesis of ht-13-A and ht-13-B, total synthesis of aurantioclavine, progress towards the synthesis of cycloclavine

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Total synthesis of ht-13-A and ht-13-B, total synthesis of aurantioclavine, progress towards the synthesis of cycloclavine.

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ABSTRACT

Total synthesis of ht-13-A and ht-13-B, total synthesis of aurantioclavine, progress towards the synthesis of cycloclavine.

Yilin Zhang

Total synthesis of tetracyclic indole alkaloid ht-13-A and ht-13-B has been accomplished from commercially available (S)-4-amino-2-hydroxybutyric acid and *trans*-4-hydroxy-L-proline respectively. The key synthetic steps include an acyliminium ion allylation, a Mitsunobu reaction, a palladium-catalyzed Stille-Kelly cross coupling reaction, and a carbon monoxide mediated palladium-catalyzed reductive *N*-heterocyclization. The total synthesis of aurantioclavine has been studied. The synthesis commenced with 2-amino-3-nitrophenol. Key synthetic steps include a Stille coupling reaction, a Heck reaction, a Lewis acid mediated cyclization and a carbon monoxide mediated palladium-catalyzed reductive *N*-heterocyclization. In addition, the first asymmetric total synthesis of (+)-cycloclavine has been studied. Key synthetic steps include a ring closing metathesis, an acyliminium ion allylation and a Stille coupling.

Dedicated to my Parents,
Kun Zhang and Yuling Sun

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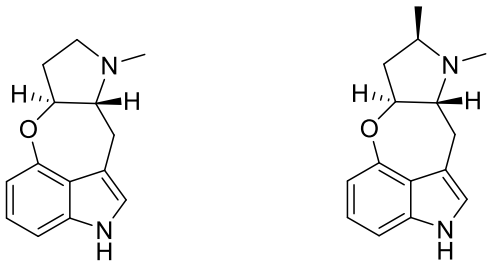
Chapter 1 Total synthesis of ht-13-B

A. Introduction

Two unique tetracyclic indole alkaloids were isolated in 2000 from *Streptomyces* sp. (PA-48561) by Kamiguchi and Yasui[1]. The alkaloids were named ht-13-A and ht-13-B, and their structures were elucidated by ^{1}H and ^{13}C NMR, UV, IR, and LRMS analyses (Figure 1). The indoles showed an affinity for serotonin receptors so that they may be used in treatment of central nervous system diseases such as depression, neurosis, senility, and Parkinson's disease. To the best of our knowledge, ht-13-A and ht-13-B are the only two examples of naturally occurring 3,4-oxepino-fused indoles and they haven't been synthesized before. Since they have very similar structural skeletons to compounds we have previously synthesized, they were chosen as target molecules by our group. A general synthetic strategy toward 3,4-fused indole alkaloids developed by our group can be applied in this synthesis which includes a Heck coupling reaction and a carbon monoxide mediated palladium-catalyzed reductive N-heterocyclization.

Figure 1 Structure of ht-13-A and ht-13-B

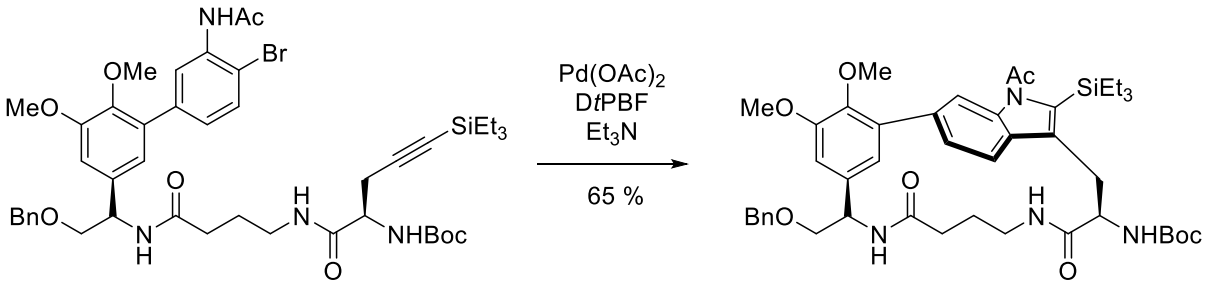


ht-13-A **ht-13-B**

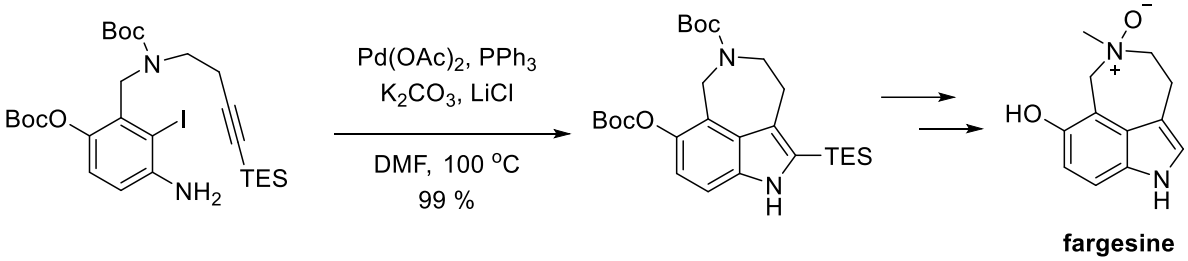
3,4-Fused indoles are usually prepared by the installation of additional ring(s) onto a preformed indole framework. Pertinent to the synthesis of ht-13-B, 3,4-oxepine-fused indoles have been prepared by intramolecular C−O coupling reactions at the 4-position of the indole skeleton via enolate O-arylation of a benzyne intermediate[2], copper-catalyzed O-arylation of an alcohol[3], and nucleophilic aromatic substitution of a 4-nitro group[4].

Scheme 1 Synthesis of 3,4-fused indoles

Boger's Synthesis :



Jia's Synthesis :



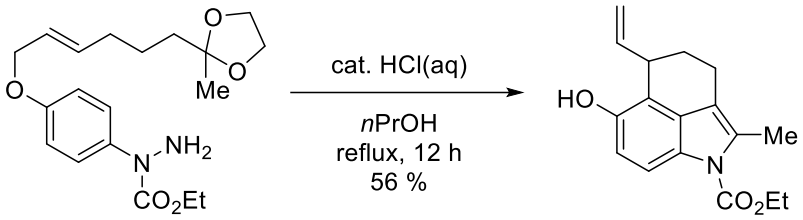
fargesine

A handful of examples have been reported wherein both the 3,4-fused ring and the pyrrole ring were sequentially assembled onto a functionalized benzene ring. This includes an intramolecular variation of the Larock indole synthesis[5,6] (Scheme 1) and an intramolecular Fischer indole synthesis (Scheme 2).[7] In addition, interesting rhodium(III)-catalyzed intramolecular amidoarylation and hydroarylation have recently been described

by three different research groups (Scheme 3).[8] We have previously reported a sequential intramolecular Heck reaction and palladium-catalyzed N-heterocyclization sequence to afford 3,4-fused indoles, including a 3,4-oxepine-fused ring system (Scheme 4).[9]

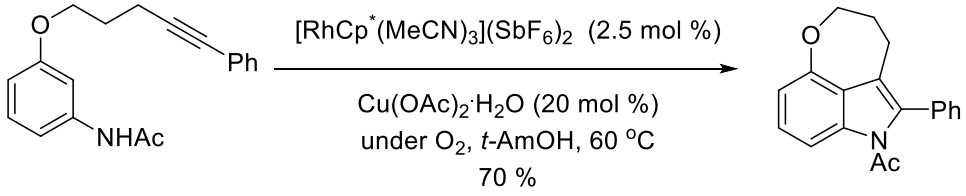
Scheme 2 Intramolecular Fischer indole synthesis

Cho's Synthesis :



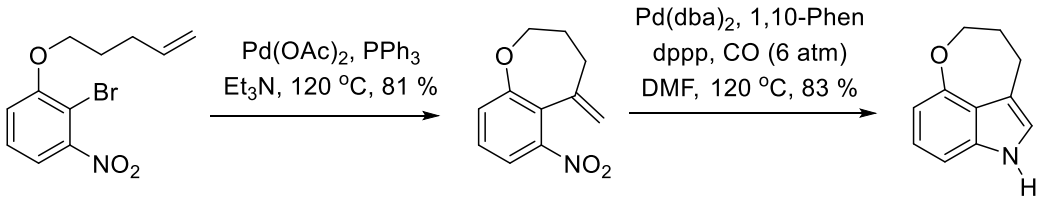
Scheme 3 Intramolecular oxidative annulation

Li's Synthesis :



Scheme 4 Intramolecular Heck reaction and N-heterocyclization

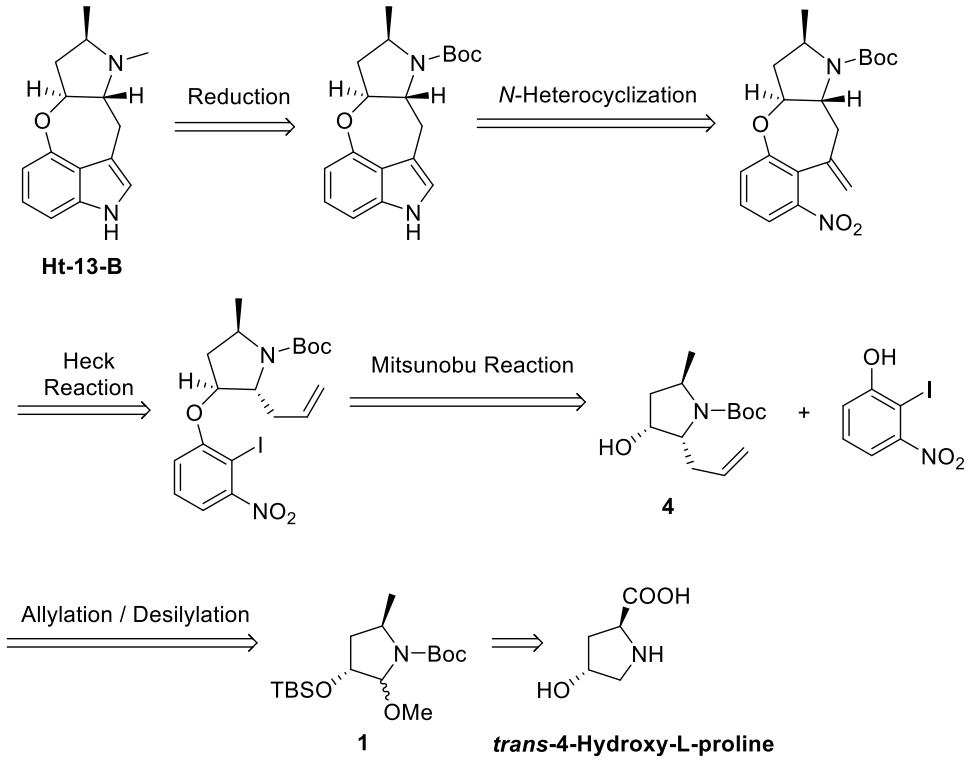
Soderberg's Synthesis :



B. Results and Discussion

The sequence depicted in Scheme 4 forms the basis of the initial retrosynthetic analysis of ht-13-B (Scheme 5). Hydride reduction of an N-alkoxycarbonyl protecting group should furnish ht-13-B. The carbamate would serve both as a protecting group limiting undesired coordination to palladium in earlier steps and as a source of the N-methyl group found in ht-13-B. In line with Scheme 4, the pyrrole ring of the indole would be formed via a palladium-catalyzed N-heterocyclization in the presence of carbon monoxide.[10] The pyrrolidine and benzene rings may be connected utilizing a Mitsunobu reaction of 2-bromo-3-nitrophenol with the allyl-substituted N-protected pyrrolidine **4** (R = t-Bu). A *trans* configuration is expected after the Mitsunobu reaction. Compound **4** was thought to be derived from diastereoselective allylation of the pyrrolidine **1** via an acyliminium ion type intermediate. Finally, pyrrolidine **1** can be achieved from commercially available *trans*-4-Hydroxy-L-proline in 9 steps according to the literature procedure.[11]

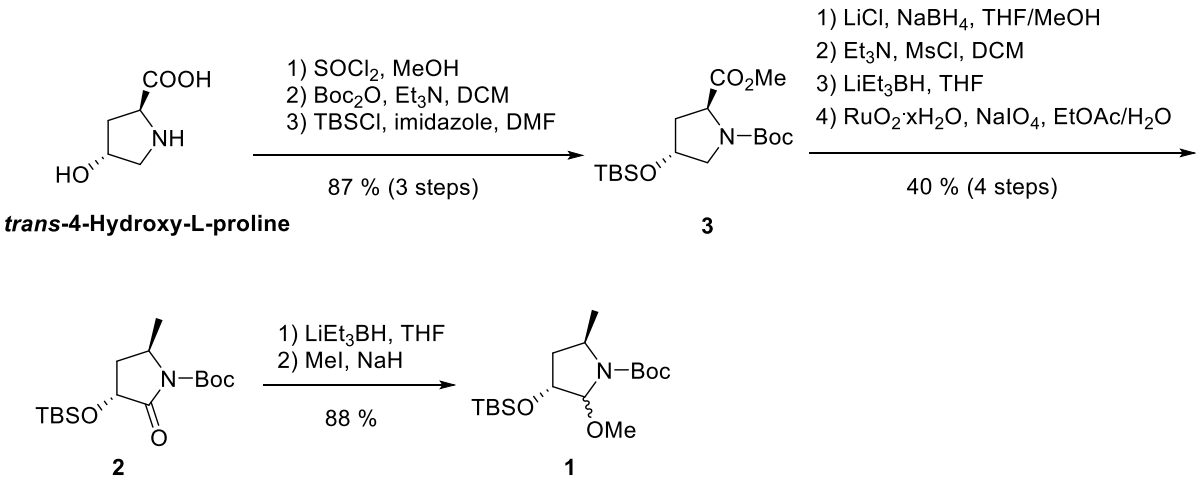
Scheme 5 Retrosynthetic analysis of ht-13-B



Pyrrolidine **1** was prepared from commercially available *trans*-4-hydroxy-L-proline following the procedure by Tanaka and Sawanishi (Scheme 6).[11] The synthesis of pyrrolidine **1** started with a methylation reaction of *trans*-4-hydroxy-L-proline using thionyl chloride in methanol. Protection of the amine and hydroxyl group with corresponding tert-butyloxycarbonyl (Boc) and tert-butyldimethylsilyl (TBS) group led to the formation of compound **3**. Treating the newly formed **3** with sodium borohydride and lithium chloride provided the corresponding alcohol, which was converted to mesylate following standard procedure. The resulting mesylate was first reduced by lithium triethylborohydride and then oxidized using ruthenium oxide and sodium periodate to yield pyrrolidin-2-one **2**. The carbonyl group in **2** was reduced by lithium

triethylborohydride and the resulting hydroxyl group was methylated using methyl iodide under basic condition to afford pyrrolidine **1**.

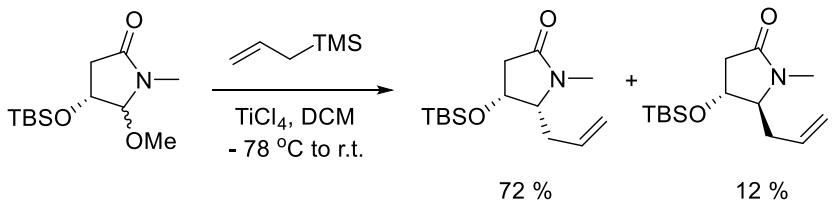
Scheme 6 Synthesis of pyrrolidine **1**[a]



[a] Prepared by colleague Jeremiah Hubbard

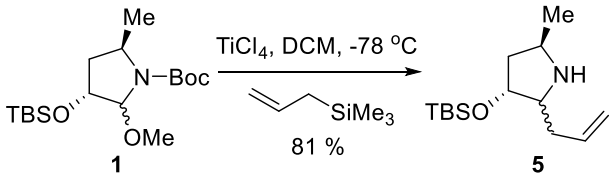
Recently, Hart and co-workers have reported a Lewis acid mediated allylation reaction from a related pyrrolidine (Scheme 7).[12] They showed that the *cis*-isomer was the major product in this reaction probably due to the directing effect of the *tert*-(butyldimethylsilyl)oxy (OTBS) group.

Scheme 7 Lewis acid mediated allylation



According to Hart's procedure, introduction of the allyl side chain was achieved using allyl trimethylsilane in the presence of titanium tetrachloride to afford **5** (Scheme 8).[12] The Boc protecting group was unexpectedly removed during the course of the reaction prior to purification.[13] In addition, the product mixture proved to be sensitive to purification by chromatography on silica gel. Compound **5** was obtained as a mixture of two inseparable diastereomers in an approximate 5:1 ratio. The stereochemistry of either isomer could not be confirmed at this point in the synthesis. However, the major isomer was expected, based on Hart's results, to have a *cis* relationship between the allyl and the OTBS groups.[11,12,14]

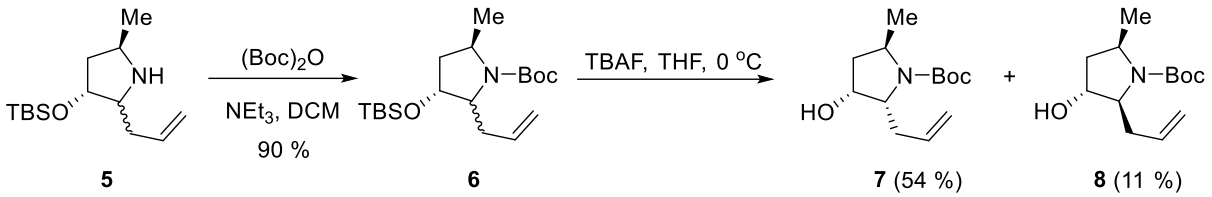
Scheme 8 Titanium tetrachloride mediated allylation



The pyrolidine nitrogen in compound **5** was reprotected using Boc_2O to give **6** (Scheme 9). We were unable to separate the isomers, and interpretation of the NMR spectra after chromatography was complicated not only by the presence of two diastereomers but also by the fact that each of the diastereomers exists as a mixture of amide bond rotamers. Removal of the *tert*-butyldimethylsilyl group using tetrabutylammonium fluoride (TBAF) afforded the diastereomeric compounds **7** and **8**. Gratifyingly, the diastereomers were readily separated by chromatography on silica gel at this point in the synthesis. The *cis* stereochemistry between the allyl chain and OTBS group in compound **7** was established by nOe NMR experiments. In addition, executing the sequence from **1** to **7** and **8** without

purification of the intermediates gave a better overall yield.

Scheme 9 Boc protection and TBAF deprotection of **5**



5 **6** **7** (54 %) **8** (11 %)

With *cis*-isomer **7** in hand, a Mitsunobu reaction was attempted in the next step. The Mitsunobu reaction was firstly reported by professor Oyo Mitsunobu in 1967.[15] It has been used in the synthesis of a variety of substrates such as esters, ethers, etc. It has been widely applied to invert the stereochemistry of an existing stereocenters in many complicate molecules.

In this synthesis, a Mitsunobu reaction of major isomer **7** with 2-bromo-3-nitrophenol **9** using triphenylphosphine and diisopropylazodicarboxylate (DIAD) gave the expected product **10** in 70 % isolated yield (Scheme 10). The inverted *trans* stereochemistry between the aryl ether and OTBS group was established by NOE NMR experiments. This in turn confirms the *cis* stereochemistry of major product **5** from the initial allylation reaction.

The Heck reaction is one of the well-known coupling reactions used in preparation of functionalized aromatic species. In the next step, an intramolecular Heck reaction[16] of **10** gave only the 8-endo trig cyclization product **11** in low isolated yield.[17,18] The expected 7-exo trig cyclization to afford **12** was not observed by ^{1}H NMR of the crude reaction mixture. Several additional catalyst systems were examined, all affording 8-endo product **11** in similar or lower isolated yields. Although the tricyclic compound cannot be used in

the synthesis of ht-13-B, the *trans* stereochemistry of the pyrrolidine-oxepine ring fusion was confirmed by single crystal X-ray analysis of **11** (Figure 2).

Scheme 10 Mitsunobu and intramolecular Heck reactions

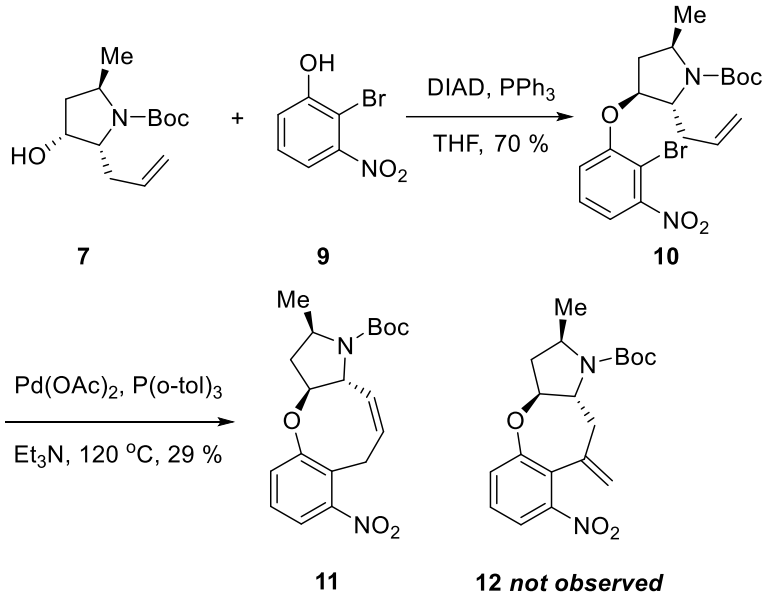
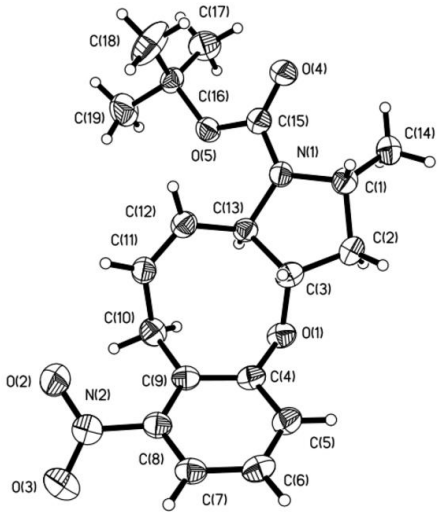
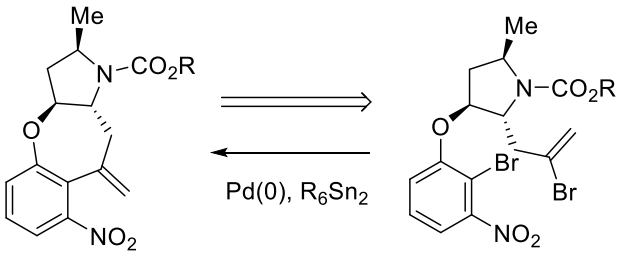


Figure 2 X-ray analysis of compound **11**



Considering the exclusive formation of 8-endo cyclization product **11** from the Heck reaction of **10**, a different approach was needed for the preparation of key intermediate **12**. Palladium(0)-catalyzed intramolecular coupling reactions of substrates containing two separate electrophilic sites (e.g., a halide or triflate) both able to undergo oxidative addition have been reported. One such coupling is the Stille-Kelly reaction.[19,20] In this reaction, one electrophilic site undergoes intermolecular palladium-catalyzed trialkylstannylation using hexaalkylditin followed by an intramolecular Kosugi-Migita-Stille reaction. This one-pot coupling reaction has mostly been used for aryl-aryl couplings,[20c,21] although coupling reactions of a few aryl electrophiles with vinyl triflates,[20a,b,22] and a vinyl bromide with a vinyl triflate,[20d] have been reported. No aryl electrophile-vinyl bromide couplings have been reported to the best of our knowledge. In contrast to the Heck reaction, the ring size of the product depends on the position of the two electrophilic sites; thus, a halide on the internal alkene carbon of the allyl group of the pyrrolidine ring should give rise to a seven-membered ring with an exocyclic alkene (Scheme 11).

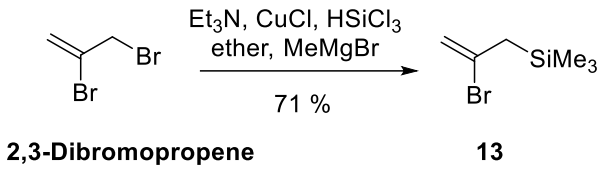
Scheme 11 Modified oxepine cyclization precursor



The new cyclization precursor was prepared in a fashion similar to compound **10**. In the Lewis acid mediated allylation reaction, an alternative allyl compound **13** was used

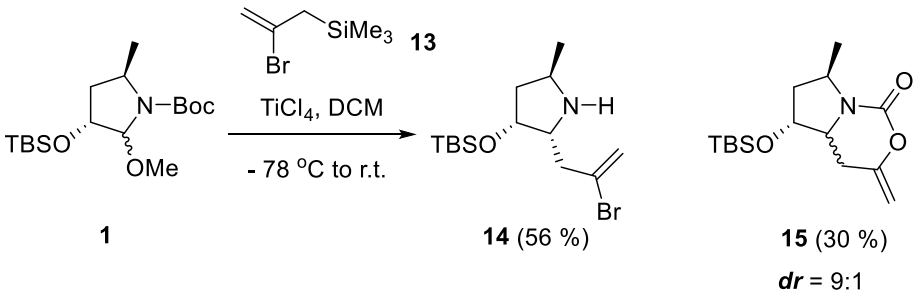
which was prepared from commercially available 2,3-dibromopropene according to the literature (Scheme 12).[23]

Scheme 12 Synthesis of 2-bromo-2-propen-1-yltrimethylsilane **13**



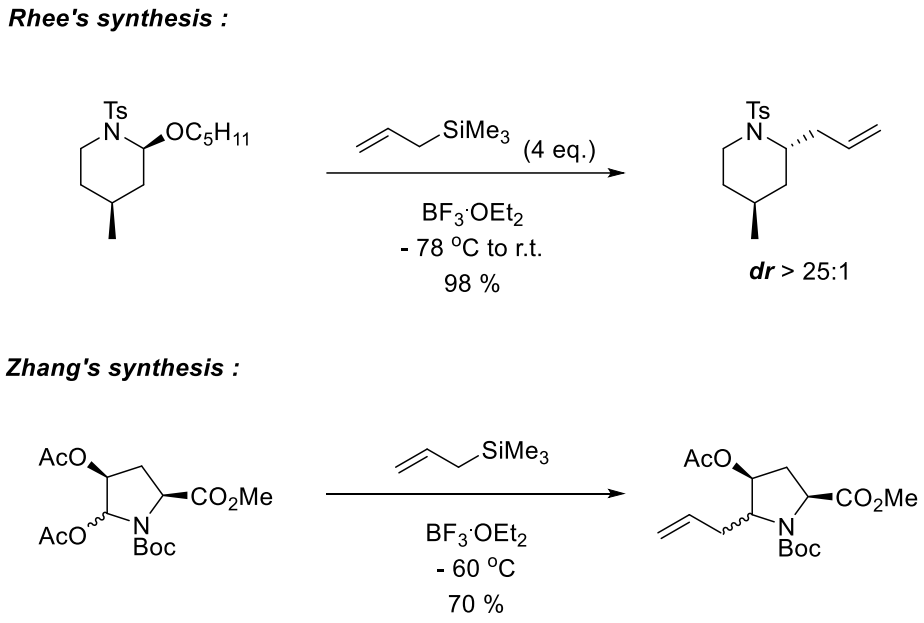
Treatment of **1** with an excess of 2-bromo-2-propen-1-yltrimethylsilane **13**[23] in the presence of titanium tetrachloride afforded allylation product **14**, again with the loss of the Boc protecting group (Scheme 13).[24] In addition to **14**, bicyclic compound **15** was also isolated as a mixture of diastereomers. Related bicyclic compounds have been reported from gold-catalyzed cyclizations between an N-Boc group and an alkyne[25] or an allene.[26] Compound **14** was isolated as a 9:1 mixture of isomers after chromatography. The relative *cis* stereochemistry between the allyl and the OTBS groups of the major isomer of **14** was elucidated by double pulsed field gradient spin echo nuclear Overhauser effect (DPFGSE-NOE) NMR experiments. It should be noted that the mixture of isomers could not be separated at any point in the synthesis prior to the final product.

Scheme 13 Synthesis of pyrrolidine **14**



Other Lewis acids have been employed in reactions of acyliminium ion intermediates with nucleophiles. For example, no loss of the Boc group was observed using boron trifluoride diethyl etherate **(**$BF_3{\cdot}OEt_2$) (Scheme 14).[14,27]

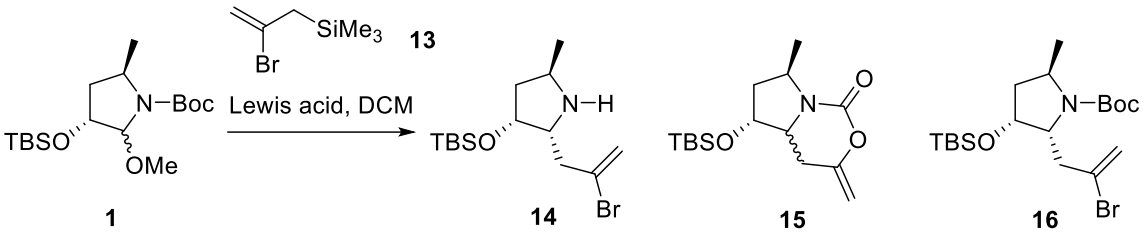
Scheme 14 Allylation without loss of Boc group



Thus, the reaction of **1** with **13** in the presence of $BF_3{\cdot}OEt_2$ as the Lewis acid and the influence of the reaction temperature was briefly investigated (Table 1). Under an identical temperature profile as used for the reaction in the presence of titanium tetrachloride ($TiCl_4$), an inferior yield of an inseparable mixture of isomeric **14** mixed with unknown side products was obtained (Table 1, entry 2). Treatment of **1** with **13** at -78 ℃ did not go to completion even after extended reaction times (Table 1, entry 3). In addition to a significant amount of starting material, a low yield of the allylated pyrrolidine **16** having an intact Boc group was isolated. Finally, all of the starting material was consumed at a higher reaction temperature (-30 ℃), but the yield of **16** was still unsatisfactory (Table 1,

entry 4). As was the case employing $TiCl_4$, a significant amount of bicyclic product **15** was also isolated. It was concluded that $BF_3{\cdot}OEt_2$ did not significantly improve the outcome of the reaction.

Table 1 Allylation of **1** using 2-bromo-2-propen-1-yltrimethylsilane **13**

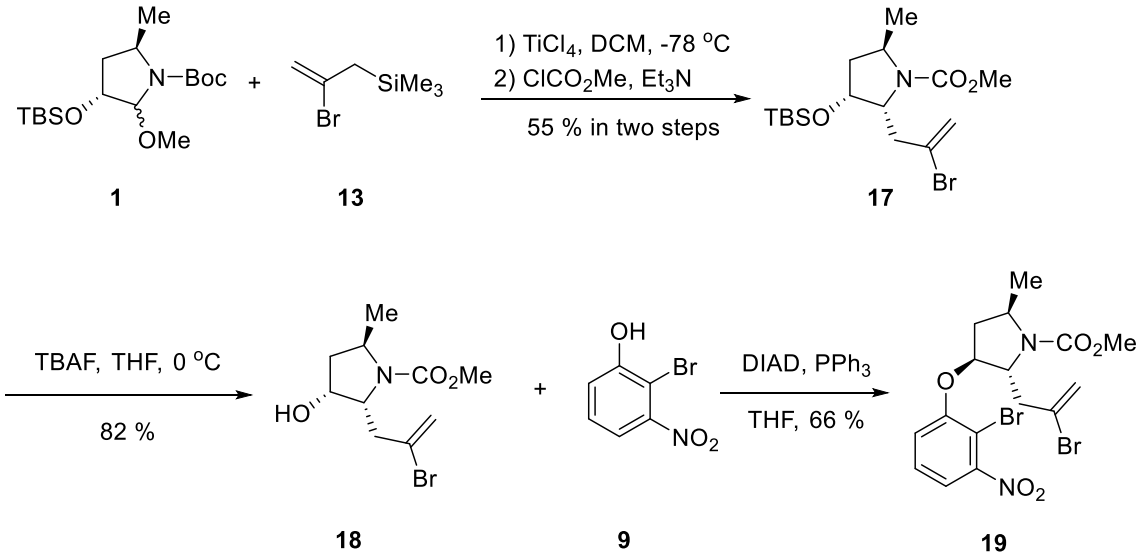


Entry	Lewis acid	Temperature	Products (% isolated yield)		
1	$TiCl_4$	-78 ℃ to r.t.	**14** (56 %)	**15** (30 %)	
2	$BF_3{\cdot}OEt_2$	-78 ℃ to r.t.	**14** (<41 %)[a]	**15** (trace)	
3	$BF_3{\cdot}OEt_2$	-78 ℃	**1** (47 %)		**16** (19 %)
4	$BF_3{\cdot}OEt_2$	-78 ℃ to -30 ℃		**15** (23 %)	**16** (43 %)

Purified amine **14** was re-protected as a methyl carbamate using methyl chloroformate to afford **14** (Scheme 15). A significantly higher overall yield of **14** from **1** was obtained without purification of crude **14** (55 % vs 23 %). Removal of the TBS group with TBAF gave compound **18**. Mitsunobu reaction was attempted in next step. Treatment of **18** with 2-bromo-3-nitrophenol **9** in the presence of 1.1 eq. of DIAD simply resulted in the recovery of starting material **18**. To our delight, the use of 4.0 eq. of DIAD in the Mitsunobu

reaction led to the formation of anticipated compound **19** in 66 % yield.

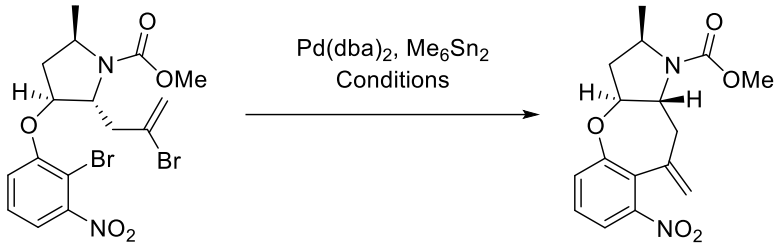
Scheme 15 Synthesis of methyl carbamate **19**



Stille-Kelly reaction of **19** with hexamethylditin in the presence of a catalyst system consisting of bis(dibenzylidenacetone)palladium(0)-triphenylphosphine produced desired tricyclic compound **20** (Table 2, entry 2). Although the starting material was completely consumed, no other products were isolated. A few additional catalyst systems were examined in an attempt to improve the yield of the reaction. However, inferior results were obtained in all cases (Table 2). Considering the two active coupling sites exists in the starting material, we believe that polymerization may occur during the transformation which gave rise to uninterpretable byproducts and lowered the isolated yield of desired product. Comparing all the conditions attempted, the Stille-Kelly reaction of **19** using PPh_3 as the ligand in toluene at 140 ℃ provided the best isolated yield (44 %) (Table 2, entry 2). Lower temperature resulted only in decomposition or polymerization of the

starting material (Table 2, entry 1). Likewise, poor yield of desired product was obtained when other ligand-solvent systems were employed (Table 2, entry 3-6).

Table 2 Stille-Kelly reaction of **19**

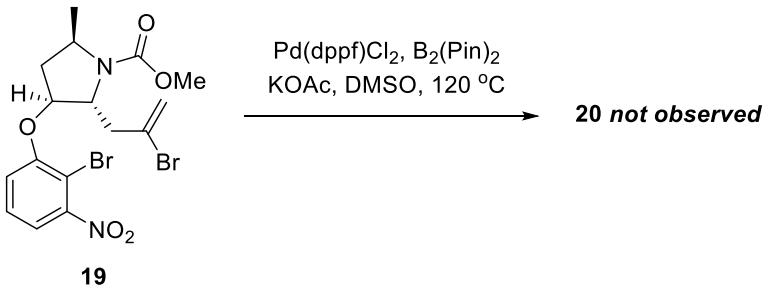


Entry	Ligand/Additive	Solvent	Temperature	Time	Yield
1	PPh_3	toluene	80 ℃	3 h	trace
2	**PPh_3**	**toluene**	**140 ℃**	**3 h**	**44 %**
3	$AsPh_3$	toluene	140 ℃	1.5 h	39 %
4	PPh_3	DMF	140 ℃	3 h	33 %
5	PPh_3	dioxane	140 ℃	5.5 h	38 %
6	PPh_3/CuI	toluene	140 ℃	7 h	21 %

As an alternative to coupling of tin reagents, a boron variant wherein one of the halides is transformed to borate followed by intramolecular Suzuki coupling has been reported, for example, using bis(pinacolato)-diborane (Scheme 16).[21,28] All attempted couplings of **19** using the latter strategy were unsuccessful, resulting only in complete loss of starting

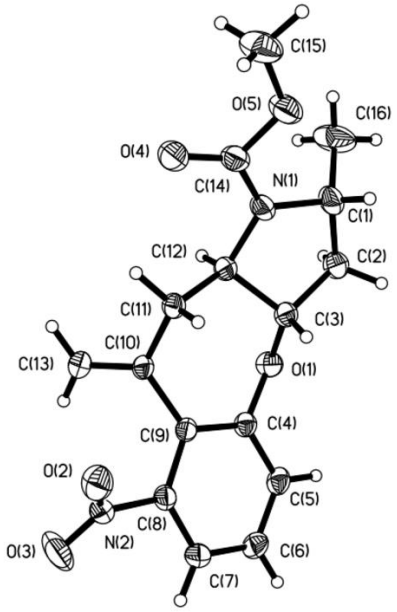
material and the formation of intractable products.

Scheme 16 Intramolecular Suzuki coupling of **19**



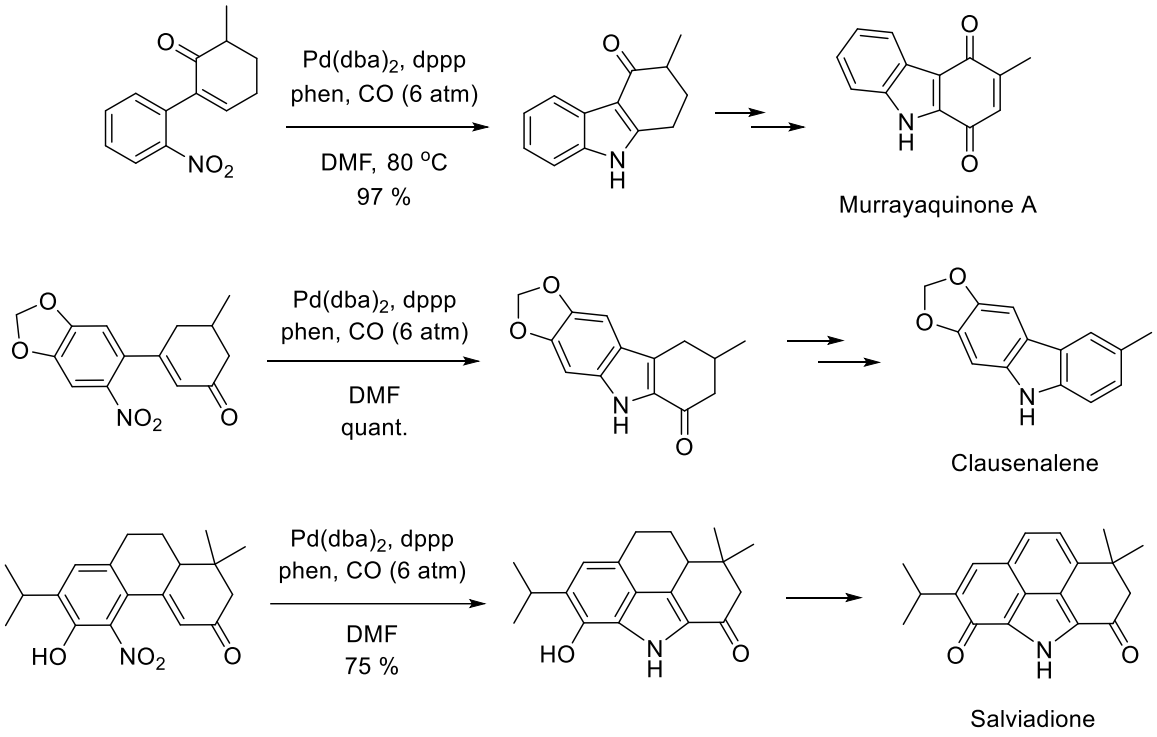
The structure and relative stereochemistry of indole precursor **20** were confirmed by extensive NMR experiments and single crystal X-ray analysis (Figure 3).

Figure 3 X-ray analysis of indole precursor **20**



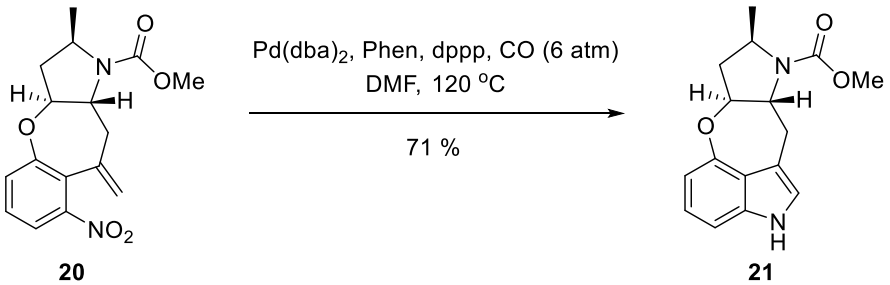
In the next step, the indole precursor **20** was subjected to a palladium-catalyzed reductive N-heterocyclization reaction developed by our group[10]. Utilizing this reaction, our group have accomplished the total synthesis of several indole natural products such as murrayaquinone A, clausenalene, and salviadione (Scheme 17).

Scheme 17 Previous synthesis using reductive N-heterocyclization reactions



As expected, N-heterocyclization of **20** gave the tetracyclic indole **21**, the immediate precursor to the alkaloid ht-13-B, as a single isomer (Scheme 18).

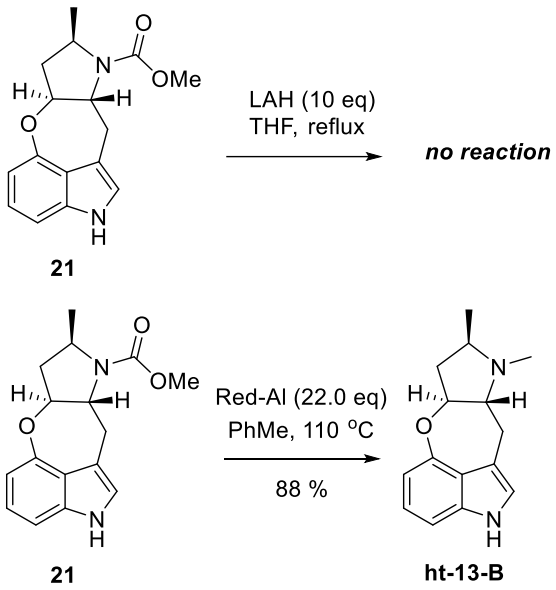
Scheme 18 Reductive N-heterocyclization of **20**



20 **21**

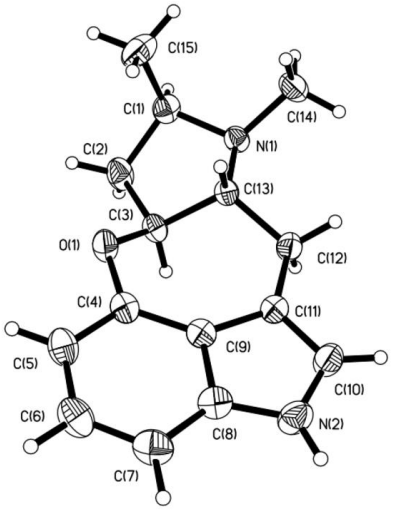
Finally, the N-methoxycarbonyl protecting group of **21** was reduced to a methyl group using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene at 110 ℃ to afford ht-13-B in high isolated yield (Scheme 19).[29] Reduction of **21** using a large excess of lithium aluminum hydride (LAH) in refluxing tetrahydrofuran (THF) was also attempted; however, this only resulted in complete recovery of the starting material.

Scheme 19 Synthesis of ht-13-B



The structure of the final product was elucidated by extensive NMR experiments and single crystal X-ray analysis (Figure 4). The NMR, IR, HRMS, melting point,[30] and optical rotation were compared with literature data, which all corroborated the originally proposed structure. The overall yield of ht-13-B in seven steps starting from compound **1** was 8 %.

Figure 4 X-ray analysis of ht-13-B



C. Conclusions

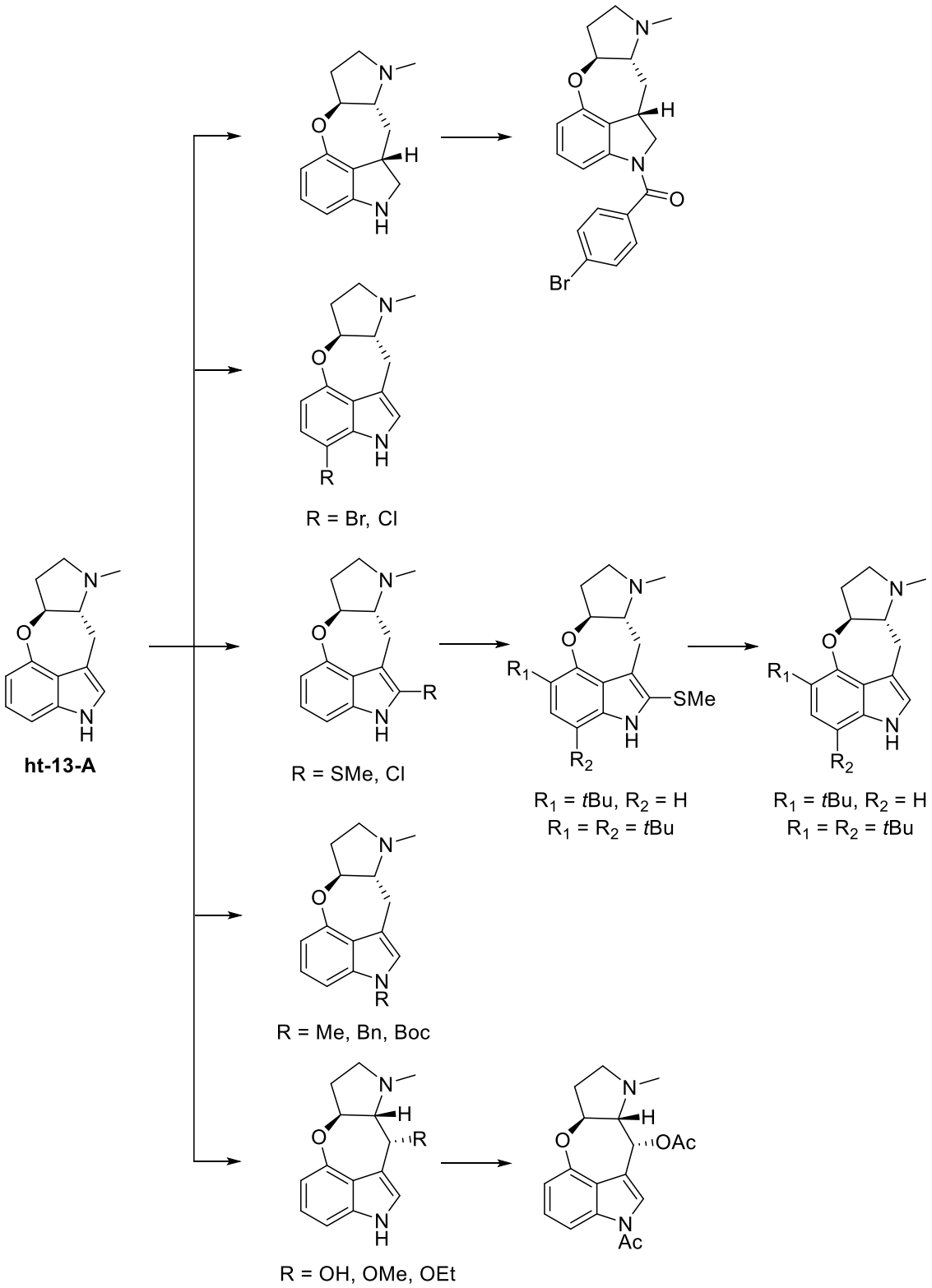
An expedient synthesis corroborating the proposed structure of the tetracyclic indole alkaloid ht-13-B has been accomplished.[31] Key synthetic steps include a Lewis acid mediated allylation, a Mitsunobu reaction, a palladium-catalyzed Stille-Kelly cross coupling reaction, and a carbon monoxide mediated palladium-catalyzed reductive N-heterocyclization. The chiral centers are ultimately derived from commercially available *trans*-4-hydroxy-L-proline.

Chapter 2 Total synthesis of ht-13-A

A. Introduction

The indole alkaloid ht-13-A has one less methyl group than ht-13-B. It was the major biosynthetic product isolated from *Streptomyces* sp. (PA-48561) according to Kamiguchi and Yasui's patent.[1] In addition, the patent claims that ht-13-A is an important starting material for the synthesis of a variety of derivatives (Figure 5) which are believed to have significant biological activities. Therefore, the proposed total synthesis of ht-13-A offers an approach for its preparation, which would be significantly beneficial to the understanding of its biological functions.

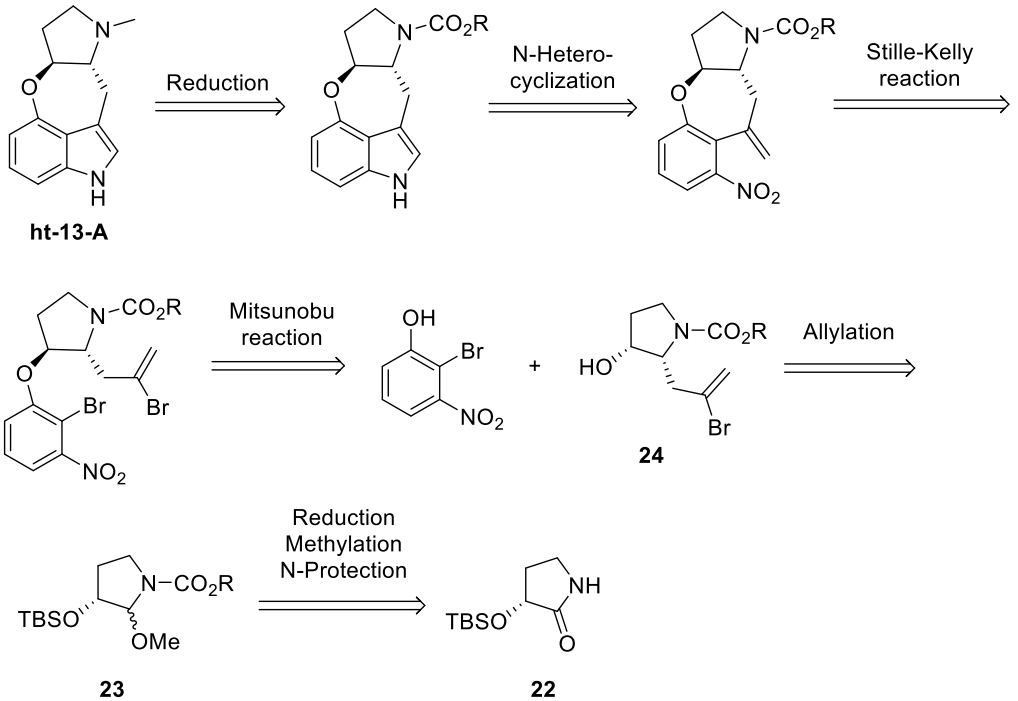
Figure 5 Derivatives of ht-13-A



B. Results and Discussions

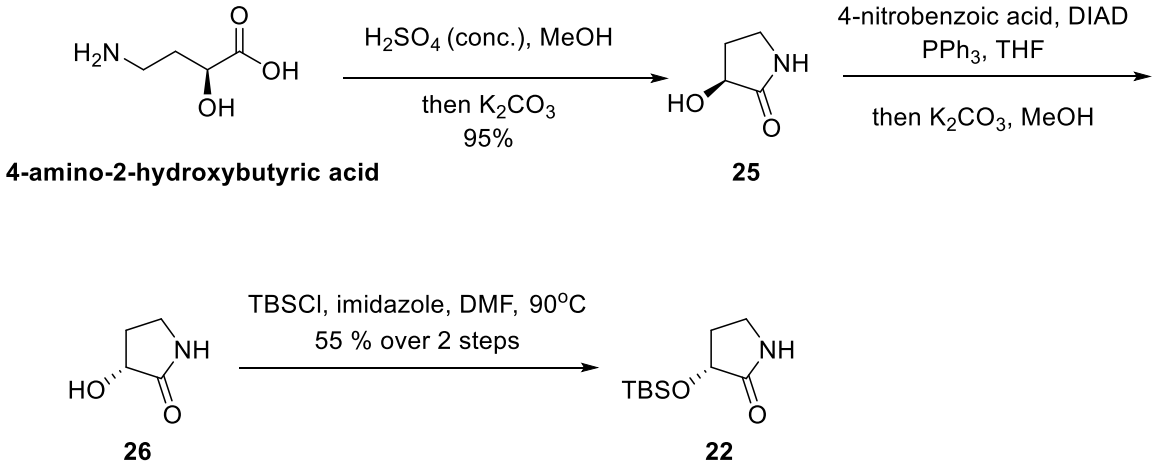
The retro-synthetic analysis of ht-13-A has been developed based on the synthetic strategy of ht-13-B (Scheme 20). The N-methyl group found in ht-13-A should be obtained from a hydride reduction of an N-alkoxycarbonyl protecting group. The palladium-catalyzed N-heterocyclization would build the desired indole core in ht-13-A. In our previous study, the 7-member ring in ht-13-B was successfully obtained via a Stille-Kelly cross-coupling reaction, whereas, a Heck cross-coupling reaction only gave an unexpected 8-endo cyclization product (Scheme 10, Table 2). Thus, in the synthesis of ht-13-A, the desired 7-exo trig cyclization product is expected after Stille-Kelly reaction. The benzene ring could be installed by a Mitsunobu reaction between 2-bromo-3-nitrophenol and the allyl-substituted N-protected pyrrolidine **24**. The pyrrolidine in turn could be prepared from diastereoselective allylation of the *N,O*-acetal species **23** which can be obtained from the known 2-pyrrolidinone **22**.

Scheme 20 Retrosynthetic analysis of ht-13-A



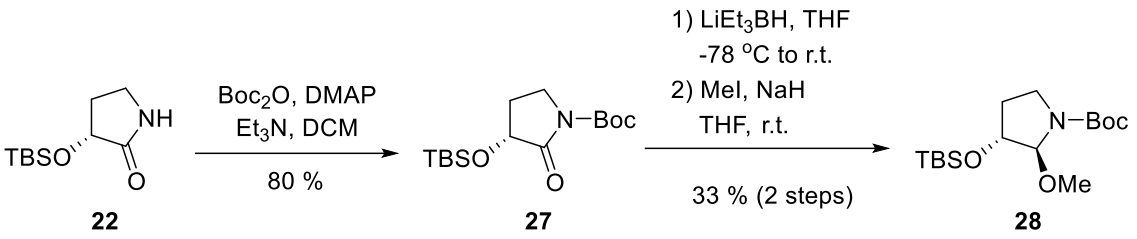
3(*R*)-*t*-Butyldimethylsilyloxypyrrolidin-2-one **22**[32] was prepared in four steps from commercially available 4-amino-2(*S*)-hydroxybutyric acid (Scheme 21). Thus, treatment of 4-amino-2(*S*)-hydroxybutyric acid with sulfuric acid in methanol followed by neutralization using potassium carbonate gave pyrrolidin-2-one **25**. Compound **25** was converted to the benzoic acid ester via a Mitsunobu reaction. The stereochemistry was reversed in this transformation. Next, pyrrolidin-2-one **26**, which has R-configuration at C-3, was formed by the saponification using potassium carbonate. The hydroxyl group was then protected as a TBS ether giving compound **22**.[33] The 3(R)-OTBS group in **22** was anticipated to be the initial source of the two chiral centers of the target molecule.

Scheme 21 Synthesis of pyrrolidin-2-one **22**



The nitrogen in pyrrolidin-2-one **22** was protected using di-*tert*-butyl dicarbonate (Scheme 22). Regioselective reduction by lithium triethylborohydride was observed at the carbonyl group on the pyrrolidinone ring of **27**. The resulting hydroxyl group was methylated using sodium hydride and methyl iodide to afford the *N,O*-acetal **28** having *trans*-stereochemistry.

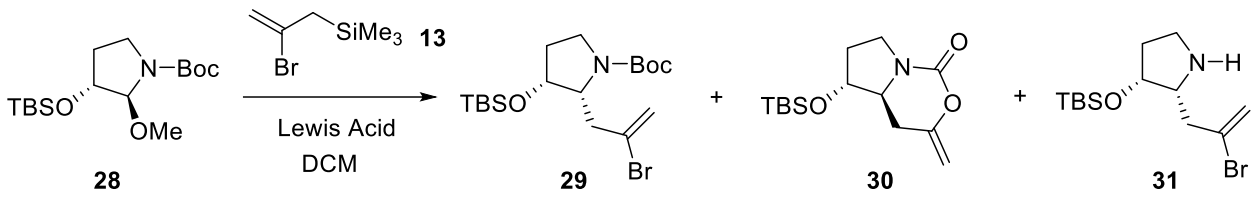
Scheme 22 Synthesis of *N*,*O*-acetal **28**



In the next step, the allyl side chain was installed via the Lewis acid mediated allylation reaction. Two different Lewis acid, boron trifluoride diethyl etherate and titanium tetrachloride were examined in this reaction and the results were compared in Table 3. Treatment of **28** with $BF_3{\cdot}OEt_2$ at -60 °C gave the *cis* allylation product as the major product (***dr*** = 6:1) without loss of the Boc protecting group (Table 3, entry 1). Herein, the stereoselectivity arose due to the directing effect of the OTBS group in **28**. Meanwhile, the minor *trans* product was converted to a bicyclic compound **30** in the same transformation. No product was isolated wherein the Boc protecting group was lost during the reaction. When compound **28** was subjected to the $TiCl_4$ condition (Table 3, entry 2), the Boc protecting group was removed and the allyl compound **31** was isolated in 50 % yield. Similar results was found in the synthesis of ht-13-B (Table 1). Compound **30** was isolated at the same time in 9 % yield as mixture of two diastereomers (***dr*** = 9:1).

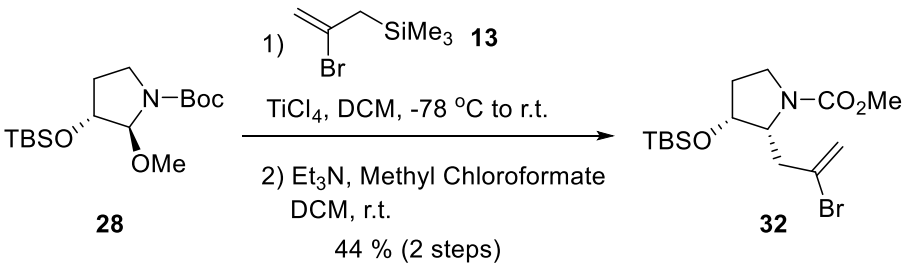
In addition, an alternative synthetic pathway was attempted in order to compare with the results in Table 3 (Scheme 23). The *N*,*O*-acetal **28** was subjected to the $TiCl_4$ mediated allylation to give **31**, which was treated with methyl chloroformate and triethyl amine without further purification to afford methyl carbamate **32**. The overall yield in two steps was 44 %.

Table 3 Lewis acid mediated allylation of **28**



Entry	Lewis Acid	Temperature	Time	**29**	**30**	**31**
1	$BF_3{\cdot}OEt_2$	-60 °C	1 h	40 % (***dr*** = 6:1)	10 %	none
2	$TiCl_4$	-78 °C to r.t.	-78 °C 15 min then r.t. 1 h	none	9 % (***dr*** = 12:1)	50 %

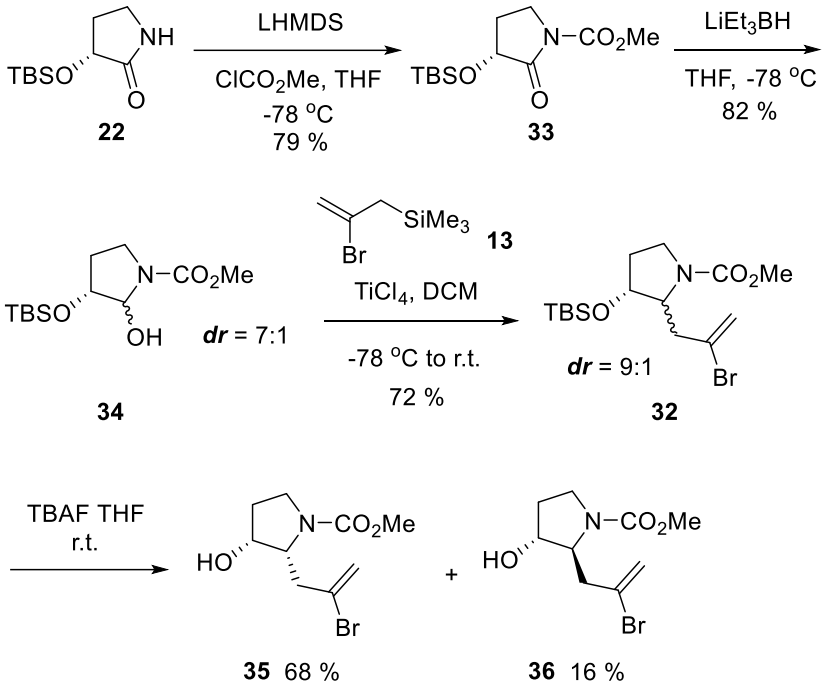
Scheme 23 Two-step procedure toward compound **32**



Because $BF_3{\cdot}OEt_2$ used in the allylation reaction gave only a moderate yield of *tert*-butyl carbamate **29**, and $TiCl_4$ used in this reaction required extra synthetic step to re-protect the amine group in the starting material, the synthetic route toward ht-13-A was modified at the early stage. In $TiCl_4$ mediated allylation reaction, another common *N*-

protecting group, methyloxycarbonyl (Moc), exhibits excellent stability. Thus, the *N*-protection of pyrrolidinone **22** using methyl chloroformate was performed following the standard procedure, giving methyl carbamate **33** in 79 % yield (Scheme 24).

Scheme 24 Synthesis of methyl carbamate **35**



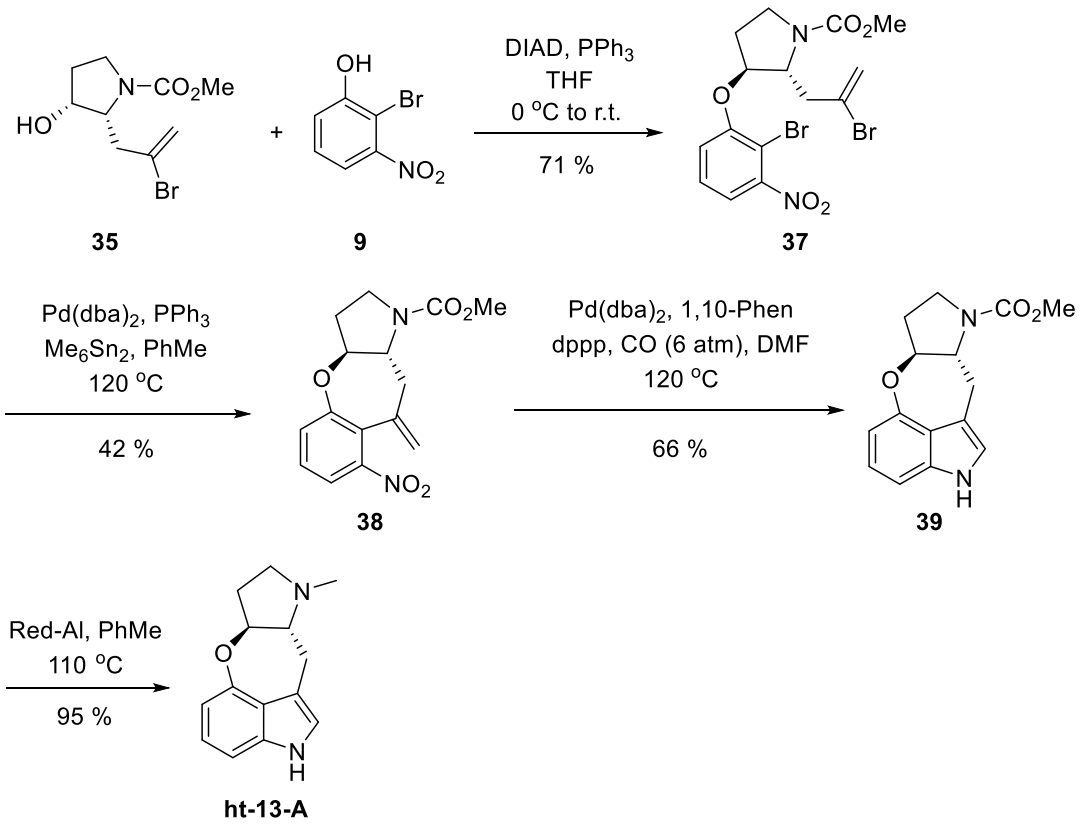
Regioselective reduction of **33** using lithium triethylborohydride gave the *N,O*-hemiacetal **34** as an inseparable mixture of diastereomers. In our previous synthesis of ht-13-B[31], a related compound was initially *O*-methylated prior to a Lewis acid mediated allylation. However, in this synthesis, introduction of the allyl side chain via an acyliminium ion was achieved directly from **34**. In the event, reaction of **34** with 2-bromo-2-propen-1-yl trimethylsilane **13**[23] in the presence of an excess of titanium tetrachloride gave compound **32** as an approximately 6:1 mixture of two inseparable diastereomers. The major isomer was predicted to have a *cis*-relationship between the allyl and the OTBS groups based on literature precedence.[11,12,13d, 24] However, the stereochemistry of either of

the isomer could not be confirmed at this point in the synthesis. The *tert*-butyldimethylsilyl group was removed using tetrabutylammonium fluoride (TBAF) and at this point the diastereomers were readily separated by chromatography on silica gel affording pure pyrrolidines **35** and **36**. The expected stereochemistry of the major isomer **35** and the minor isomer **36** was *cis* and *trans*, respectively, as confirmed by nOe NMR experiments.

Mitsunobu reaction of the major isomer **35** with 2-bromo-3-nitrophenol **9** in the presence of triphenylphosphine and diisopropylazodicarboxylate (DIAD) furnished compound **37** (Scheme 25). The expected *cis* to *trans* inversion of stereochemistry was again confirmed by nOe NMR experiments. With the correct stereochemistry established, two sequential palladium catalyzed reactions were employed to build the oxepane and pyrrole rings of ht-13-A. The oxepane was obtained using an intramolecular Stille-Kelly[19] reaction. Compound **37** was treated with hexamethylditin in the presence of a catalyst system consisting of bis(dibenzylidenacetone)palladium-triphenylphosphine producing the tricyclic compound **38**. All attempts to improve the yield of the coupling reaction from **37** to **38**, by modification of the catalyst system and the reaction conditions, failed to improve the yield. In addition to palladium based systems, bis(1,5-cyclooctadiene)nickel catalyzed intermolecular cross coupling reactions between aromatic bromides have recently been reported.[34] However, the same catalyst system in this transformation only resulted in decomposition of the starting material to an intractable mixture. Palladium catalyzed reductive *N*-heterocyclization of **38** in the presence of carbon monoxide gave the expected tetracyclic indole **39**.[10] Finally, the methoxycarbonyl group was reduced to a methyl group using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene affording ht-13-A in high isolated yield. The ^{1}H and ^{13}C NMR, IR, HRMS,

melting point and optical rotation data of synthetic ht-13-A were identical to the literature values of the compound isolated by Kamiguchi and Yasui.[1]

Scheme 25 Synthesis of ht-13-A



C. Conclusions

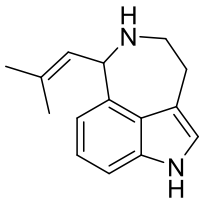
In summary, a total synthesis of the tetracyclic indole alkaloid ht-13-A was achieved starting from commercially available (-)-4-amino-2-hydroxybutyric acid. The overall yield of ht-13-A in eight steps from pyrrolidinone **22** was 6 %. The *trans* stereochemistry was obtained from an acyliminium ion allylation followed by a Mitsunobu reaction. The 7-membered oxepane ring was obtained via an intramolecular Stille-Kelly reaction and the pyrrole ring was synthesized in a late stage carbon monoxide mediated palladium catalyzed reductive *N*-heterocyclization. This synthesis exemplifies a strategy for the synthesis of 3,4-fused indole alkaloids via nitrostyrene precursors.

Chapter 3 Total synthesis of aurantioclavine

A. Introduction

(-)-Aurantioclavine was firstly isolated from *Penicillium aurantiovirens* in 1981 by Kozlovskii and co-workers.[35] (-)-Aurantioclavine is one of a number of 3,4-fused indole alkaloids containing a 7-membered azepino ring as well as a R chiral center (Figure 6). It has been proven to be an important intermediate in the biosynthesis of communesin family natural products.

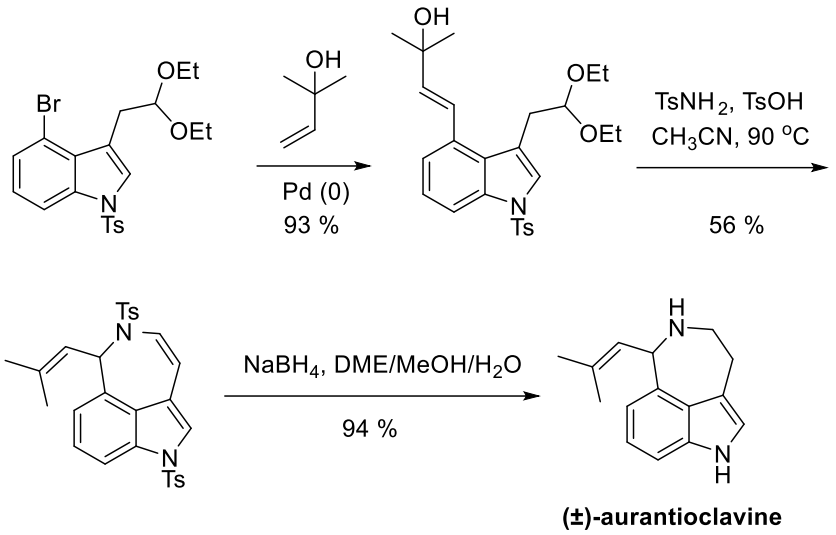
Figure 6 Structure of aurantioclavine



aurantioclavine

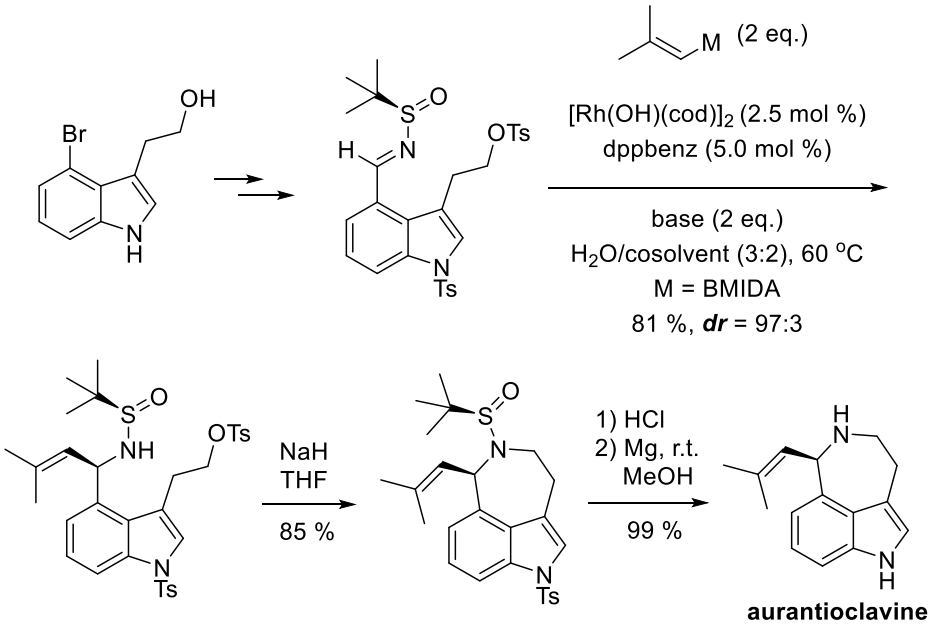
After its discovery, several total synthesis pathways of this molecule have been designed.[36] The first synthesis of aurantioclavine was reported by Hegedus and co-workers in 1987 (Scheme 26). In their synthetic strategy, the C-4 side chain was installed through a Heck coupling and then the 7-membered ring found in aurantioclavine was obtained via an acid-catalyzed intramolecular cyclization. Finally, the synthesis of aurantioclavine was completed after removal of a tosylate. The overall yield of aurantioclavine was 23 % in 13 steps from a commercially available compound.

Scheme 26 Hegedus's synthesis of aurantioclavine



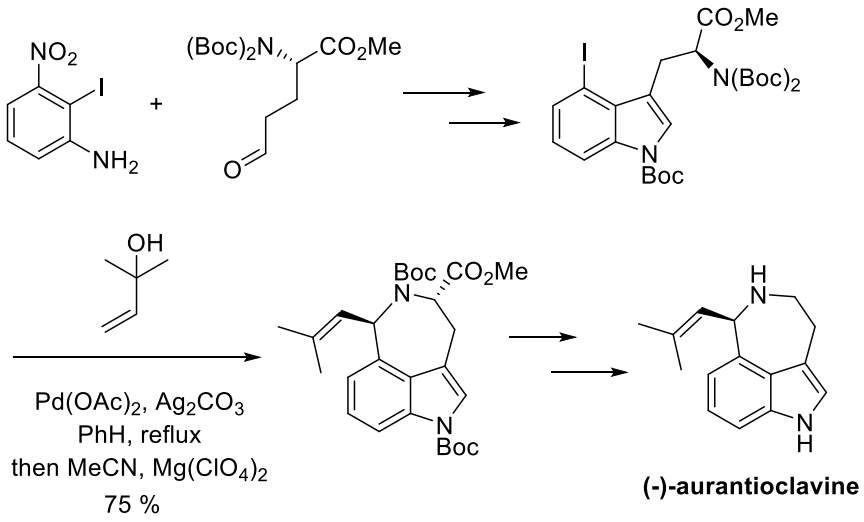
In 2010, Ellman and co-workers reported an asymmetric total synthesis of aurantioclavine starting with 4-bromotryptophol (Scheme 27). The chiral center was obtained from an asymmetric alkenylation of an N-*tert*-butanesulfinyl imine intermediate. The desired 7-member ring was built in the late stage via a basic substitution reaction.

Scheme 27 Ellman's synthesis of (-)-aurantioclavine



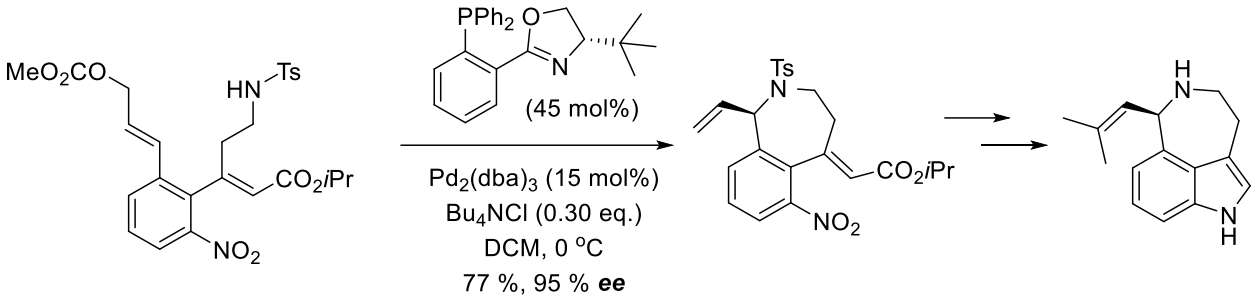
In the same year, Jia and co-worker reported another asymmetric synthetic strategy toward (-)-aurantiocalvine (Scheme 28). The chiral center in the molecule was derived from methyl (S)-2-di-*tert*-butoxycarbonylamino-5-oxopentanoate. The structural skeleton of aurantioclavine was accomplished through a one pot Heck-aminocyclization reaction.

Scheme 28 Jia's synthesis of (-)-aurantioclavine



Recently, Takemoto's group has developed a novel asymmetric allylic amination reaction to complete the synthesis of (-)-aurantiocalvine (Scheme 29). Using (S)-*t*Bu-PHOX as the chiral ligand in this reaction furnished the desired 7-member ring with 95 % enantiomeric excess.

Scheme 29 Takemoto's synthesis of (-)-aurantioclavine

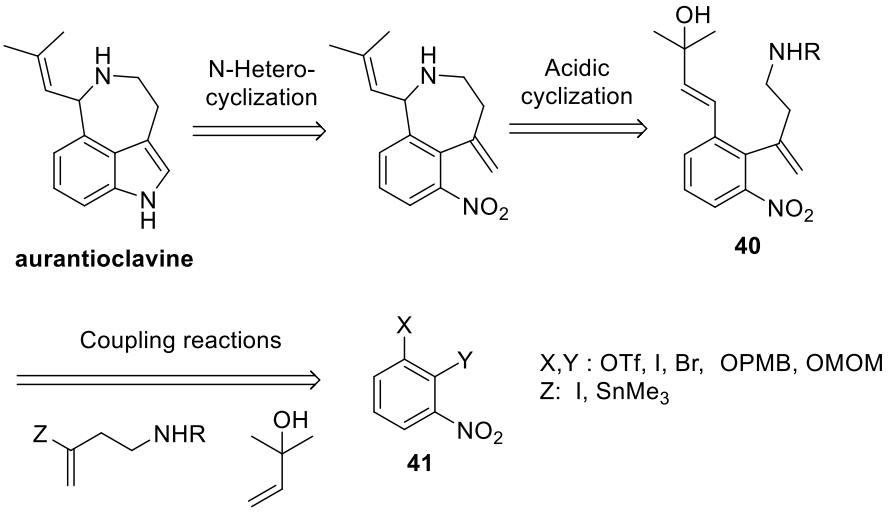


B. Results and Discussions

Most of the previous syntheses of aurantioclavine started with a preformed indole framework. It is essential to protect the nitrogen in the indole core to avoid side reactions and this requires additional synthetic steps.

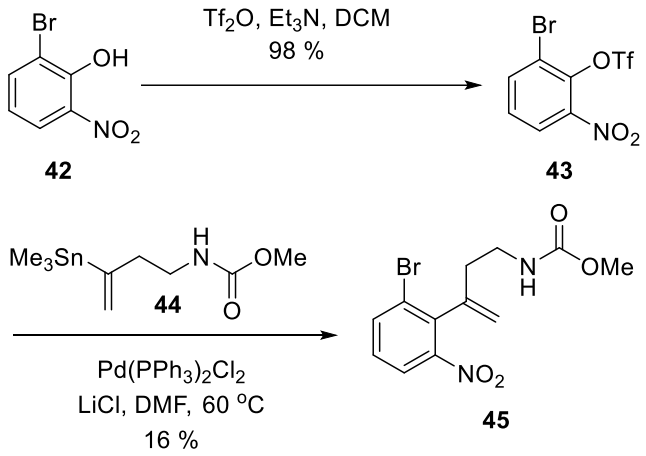
Herein, we present a shorter synthetic pathway to aurantioclavine (Scheme 30). Although a similar strategy as Takemoto's was employed, our approach avoided the extra steps necessary in their synthesis to prepare the propenyl group and the indole core. The strategy proposed is as following. The indole core should be prepared from the palladium catalyzed N-heterocyclization of a nitrostyrene precursor. The 7-member azepino ring could be generated through a Lewis acid mediated intramolecular cyclization. The two side chains in intermediate **40** may be derived from nitrobenzene **41** via metal catalyzed cross-coupling reactions.

Scheme 30 Retrosynthetic analysis of aurantioclavine



The synthesis commenced with installation of the side chains onto nitrobenzene **41** via a regioselective Kosugi-Migta-Stille coupling reaction. Phenol **42** was firstly prepared from commercially available 2-bromophenol according to a literature procedure.[37] Treatment of **42** with triethylamine and trifluoromethanesulfonic anhydride in methylene chloride gave triflate **43** (Scheme 31), which was subsequently reacted with methyl carbamate **44**[38] prepared from 3-butyn-1-ol. This cross coupling reaction was carried out using a bis(triphenylphosphine)-palladium(II) dichloride and lithium chloride system. As expected, selective coupling at the OTf position was observed. Although the correct regioselectivity was established, the Heck precursor **45** was isolated in a relatively low yield (19%), which may be caused by the steric hindrance encountered at the OTf position.

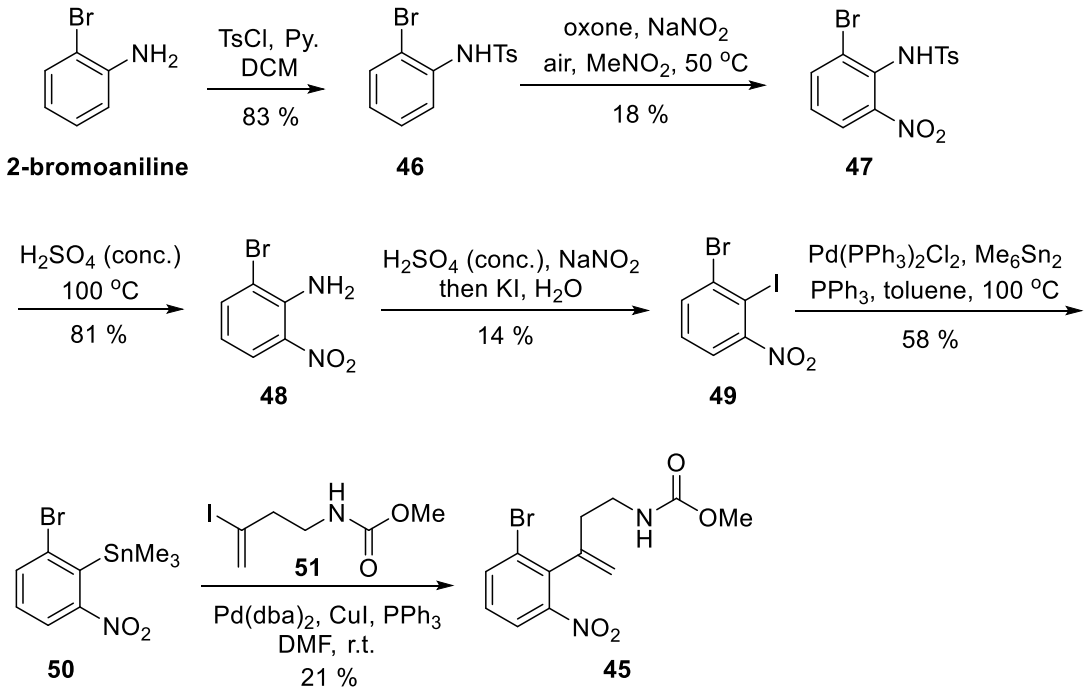
Scheme 31 Synthesis of Heck precursor **45**



Since a low yield was observed in the above coupling, an alternative pathway was investigated toward building block **45**. The synthesis started with commercially available 2-bromoaniline (Scheme 32). Protection of the amino group in 2-bromoaniline using 4-toluenesulfonyl chloride (TsCl) gave tosylate **46**. Based on a recently described nitration[39],

46 was converted to nitrobenzene **47**. Next, the tosyl group was removed using sulfuric acid and the resulting aniline **48** was transformed to 1-bromo-2-iodo-3-nitrobenzene **49** by a Sandmeyer-type reaction. Arylstannane **50** was obtained from **49** using hexamethylditin. Finally, compound **50** was subjected to the Stille coupling condition with the known methyl carbamate **51**[38], however, an inferior yield of **45** was observed again.

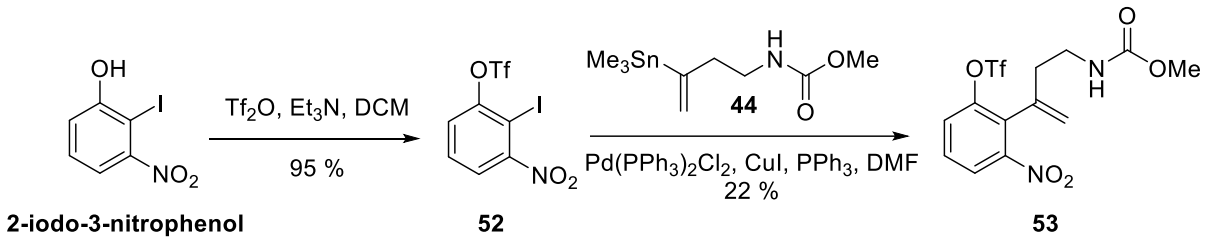
Scheme 32 Alternative pathway toward Heck precursor **45**



Since all attempts to improve the yield of **45** were unsuccessful, the following work was focused on synthesis of a similar Heck precursor **53** (Scheme 33). Triflate **52** was prepared from 2-iodo-3-nitrophenol following the standard procedure. Kosugi-Migita-Stille coupling using methyl carbamate **44** gave the desired Heck precursor **53**. Unfortunately, the yield was still unsatisfactory. All efforts using selective Stille coupling reaction for the synthesis of the Heck precursors made no contribution to the improvement

of reaction yield. The reason might be the slow reaction rate of the transmetalation in Stille coupling due to a steric hindrance problem.

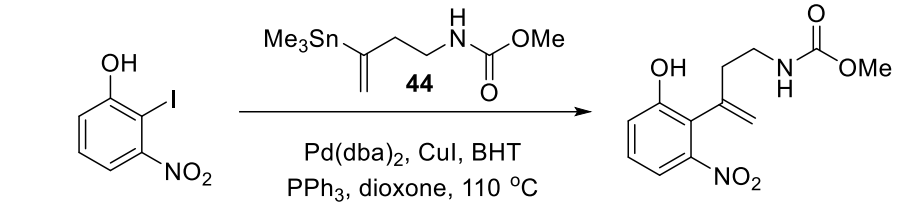
Scheme 33 Synthesis of triflate **53**



2-iodo-3-nitrophenol **52** **53**

In addition, 2-iodo-3-nitrophenol was subjected to Stille coupling condition with methyl carbamate **44** (Scheme 34). Since the unprotected hydroxyl group may cause numerous side reactions, the desired phenol **54** was isolated in a low yield.

Scheme 34 Synthesis of phenol **54**

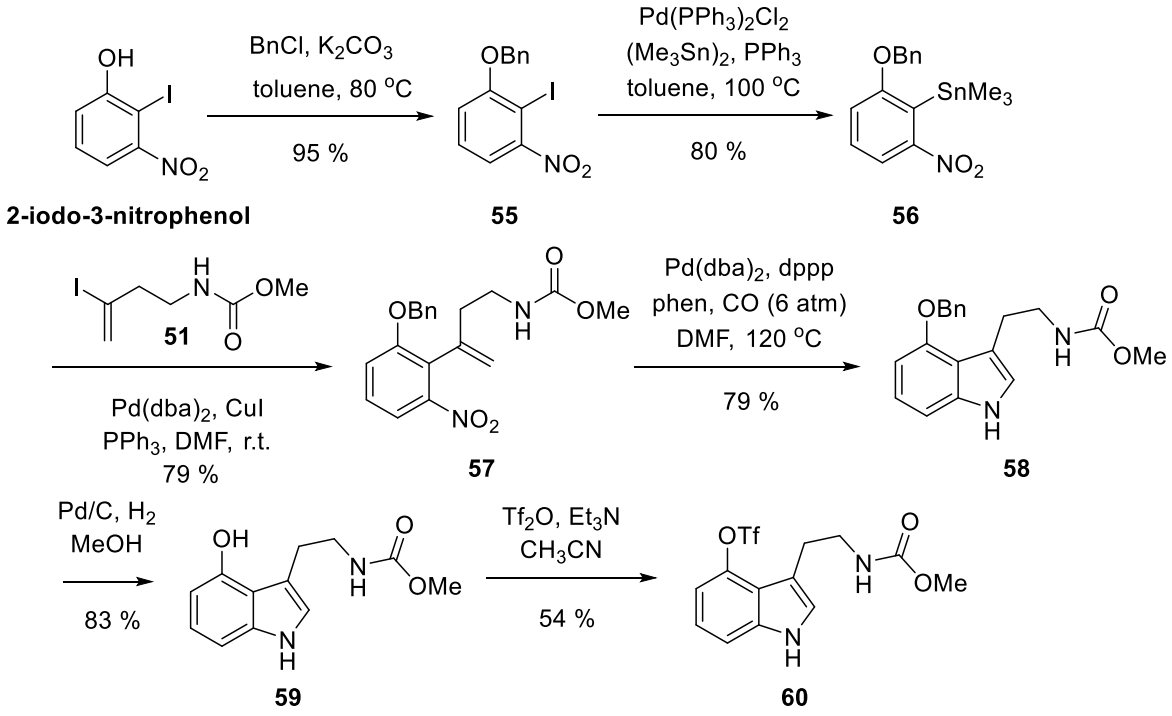


2-iodo-3-nitrophenol **54**

Considering the unsatisfactory yield of **54** found in the above coupling, a protecting group for the hydroxyl in 2-iodo-3-nitrophenol was introduced to avoid possible side reactions (Scheme 35). Protection of the hydroxyl group using benzyl chloride and potassium carbonate gave nitrobenzene **55** in high yield. Compound **55** was transformed to arylstannane **56** using hexamethylditin in the presence of bis(triphenylphosphine) palladium dichloride. Pleasingly, the Stille coupling between **56** and methyl carbamate **51**

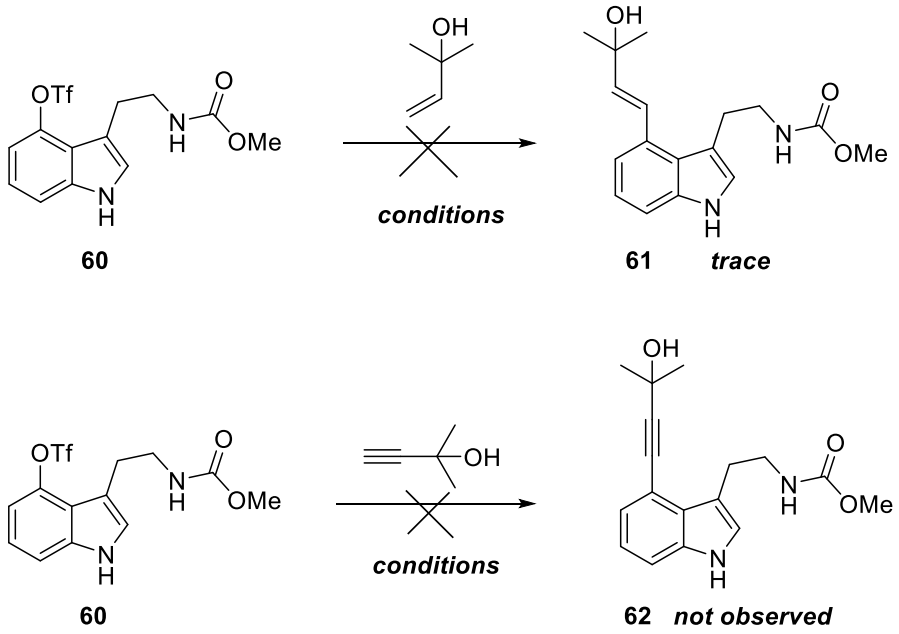
successfully accomplished the desired 2-nitrostyrene **57** in good yield. As removal of the benzyl at this point may lead to a reduction of the vinyl group and unexpected loss of methyloxycarbonyl protecting group, **57** was transformed to indole **58** first under the N-heterocyclization condition previously developed in our group.[10] With indole **58** in hand, the reactions focused on functionalization of C-4 on the indole core were examined. The benzyl protecting group was smoothly removed using 10 wt.% palladium on carbon in the presence of hydrogen gas. An alternative deprotection was examined using palladium and ammonium formate in absolute ethanol, resulting in unexpected removal of the methyloxycarbonyl group. Next, 4-hydroxyindole **59** was converted to triflate **60**. When methylene chloride was used as solvent in this transformation, extremely low yield was found probably due to the very low solubility of **59** in this solvent. Gratifyingly, using acetonitrile as solvent led to formation of triflate **60** in better yield.

Scheme 35 Synthesis of triflate **60**



We next turned attention to the construction of side chain at C-4 using a Heck reaction (Scheme 36). However, only a trace amount of product was found under various Heck conditions. The failure of those Heck coupling methods prompted us to pursue a synthesis of **61** to 2 steps, namely introducing a propargyl alcohol **(62)** which could be reduced to **61**. Unfortunately, no desired product **62** was formed under Sonogashira conditions.

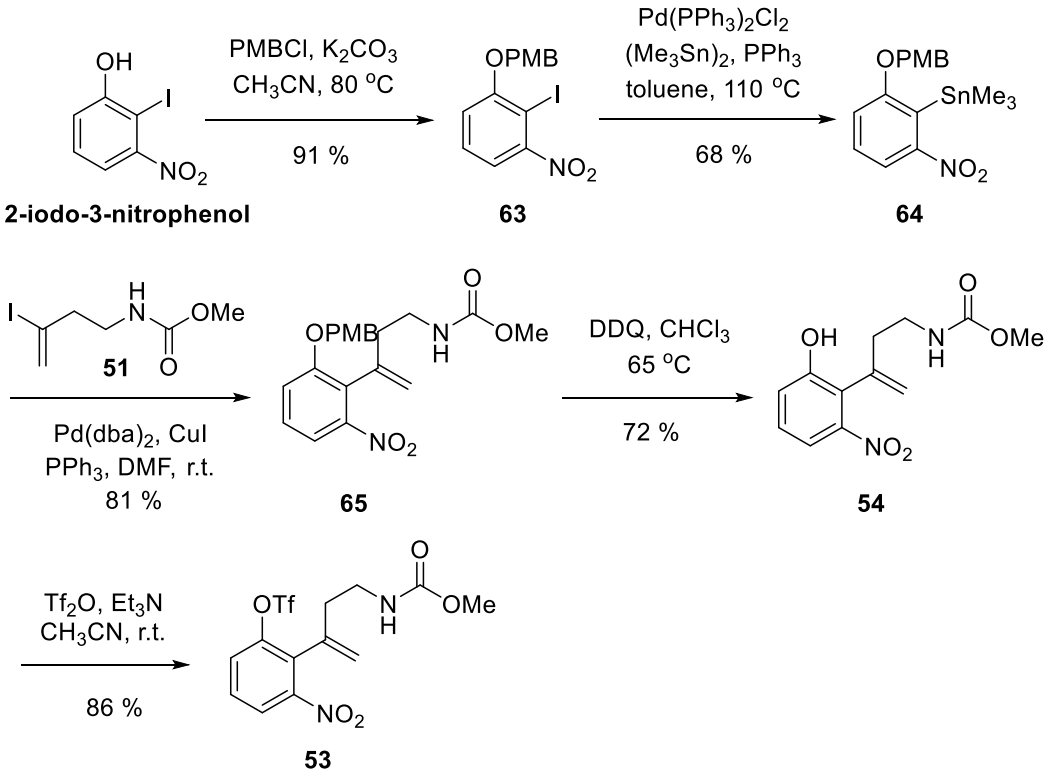
Scheme 36 Heck and Sonogashira coupling of **60**



As none of the coupling product was obtained from indole **60**, we came back to the building block **53**. Instead of using a benzyl protection approach, we anticipated that 4-methoxybenzyl protection might give the desired building block **53** via a concise procedure (Scheme 37). Reaction of 2-iodo-3-nitrophenol with a mixture of 4-methoxybenzyl chloride and potassium carbonate in refluxing acetonitrile gave 4-methoxybenzyl phenyl ether **63**. Arylstannane **64** was obtained when **63** was treated with bis(triphenylphosphine)palladium dichloride, hexamethylditin and triphenylphosphine in

refluxing toluene. Reacting arylstannane **64** with methyl carbamate **51** under standard Kosugi-Migita-Stille conditions produced **65** in 81% yield. In order to selectively remove the 4-methoxylbenzyl protecting group, **65** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing chloroform. When this deprotection was performed at ambient temperature, none of desired **54**, only starting material was recovered. Furthermore, the yield of **54** decreased significantly upon scaled-up of the reaction. Next, triflate **53** was easily obtained from **54** in 86% yield.

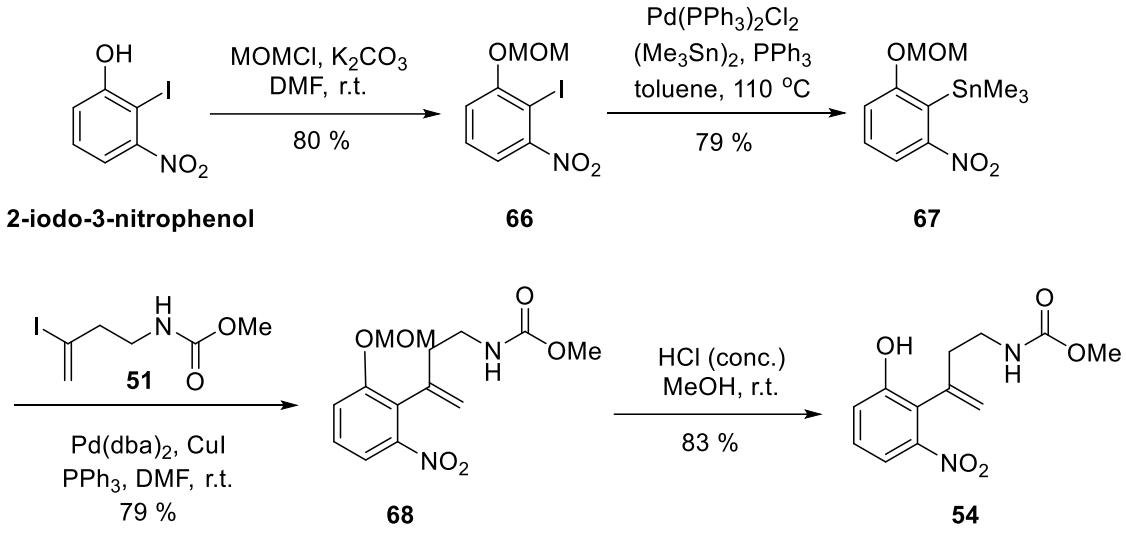
Scheme 37 Synthesis of building block **53**



Because of the failure in the removal of PMB group in the scaled-up reaction, an alternative pathway to **54** has been studied (Scheme 38). Methoxymethyl phenyl ether **66** was prepared by reacting 2-iodo-3-nitrophenol with chloromethyl methyl ether and

potassium carbonate in DMF at room temperature. Under the same condition as described for the synthesis of compound **64**, arylstannane **67** was obtained in 74% yield from **66**. Through a Kosugi-Migita-Stille coupling, arylstannane **67** was converted to 2-nitrostyrene **68**. The latter successfully lost the methoxy methyl (MOM) protecting group using concentrated HCl in methanol. Gratifyingly, the scaled-up reaction from **68** to **54** was accomplished in a comparable yield.

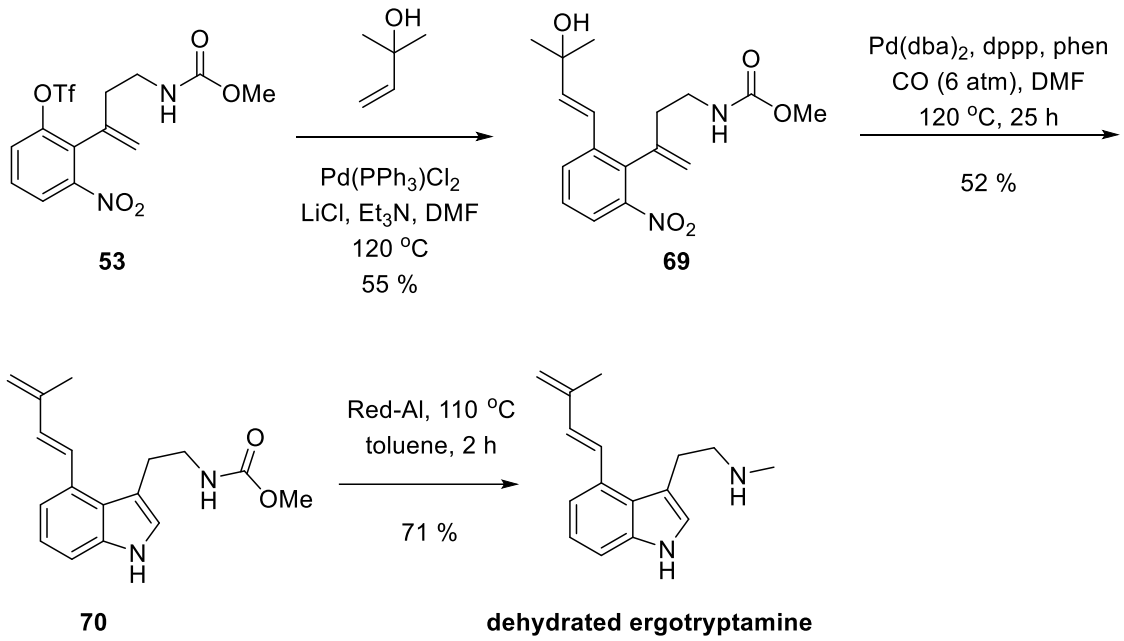
Scheme 38 Alternative pathway toward **54**



In previous reactions, it was found that iodole **60** was unreactive under Heck reaction conditions. Therefore, 2-nitrostyrene **53** was examined as a possible substrate for the installation of C-4 side chain (Scheme 39). As expected, compound **69** was readily obtained in 55% yield via the Heck reaction between triflate **53** and 2-methyl-3-buten-2-ol. Next, the indole core was successfully prepared through the N-heterocyclization reaction, whereas, dehydration occurred at the same time due to the harsh reaction condition, resulting in a formation of diene **70**. To our delight, reduction of methyloxycarbonyl group in **70** using

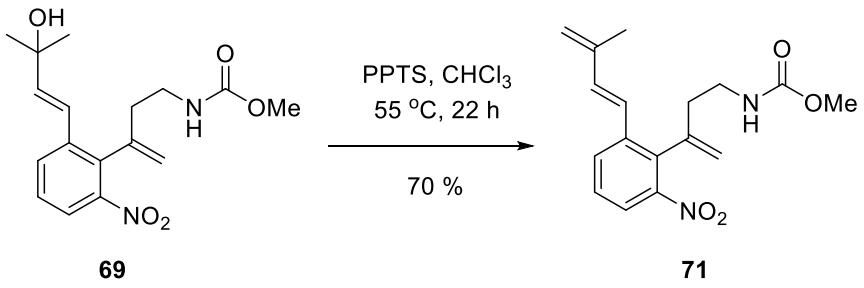
sodium bis(2-methoxyethoxy)-aluminumhydride in reflux toluene formed another natural product, dehydrated ergotryptamine isolated in 2015 by Panaccione.[39]

Scheme 39 Synthesis of dehydrated ergotryptamine



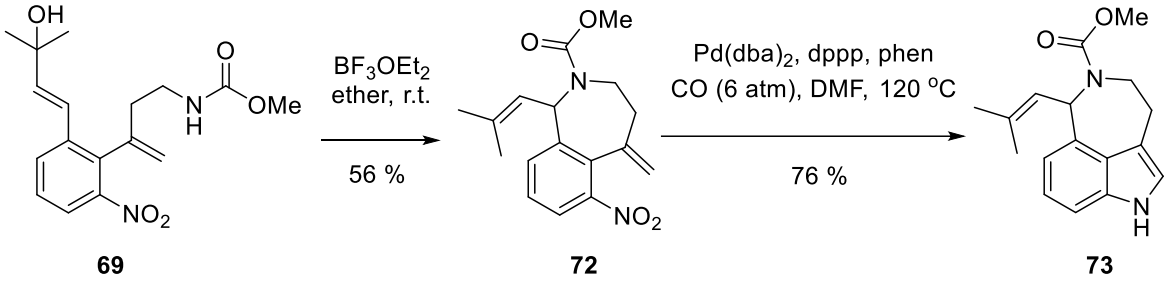
As mentioned, the N-heterocyclization performed prior to the generation of 7-membered azepino ring caused unexpected dehydration, therefore attempts were made to cyclize the 7-membered ring prior to indole formation. Treating compound **69** with pyridinium p-toluenesulfonate (PPTS) in chloroform at 55 °C again resulted in dehydration affording product **71** (Scheme 40). Gratifyingly, the desired cyclization product **72** was formed when **69** was subjected to a Lewis acid ($BF_3{\cdot}OEt_2$) in ether at ambient temperature (Scheme 41). The N-heterocyclization of **72** successfully furnished indole **73** which contained the basic framework of aurantioclavine.

Scheme 40 Failed intramolecular cyclization of **69**



69 **71**

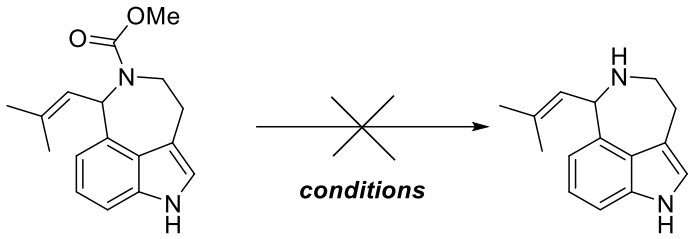
Scheme 41 Synthesis of indole **73**



69 **72** **73**

Finally, the Moc deprotection of methyl carbamate **73** was attempted to finish the synthesis of aurantioclavine. As summarized in Table 4, several conditions were examined, however, no satisfactory results were obtained. Treatment of **73** with trimethylsilyl chloride with sodium iodide or trimethylsilyl iodide only caused decomposition of the starting material (Table 4, entry 1 and 2). When **73** was exposed to the condition in entry 3, only starting material was recovered because of the low solubility of **73** in methanol. The solubility of **73** was highly improved when 1-propanol was used as solvent in this reaction, however, no desired product was found either (Table 4, entry 4). Other basic reagents including methyllithium and lithium triethylborohydride (Table 4, entry 5-7) were tried in this reaction, but none of them afforded the desired product.

Table 4 Moc deprotection of **73**



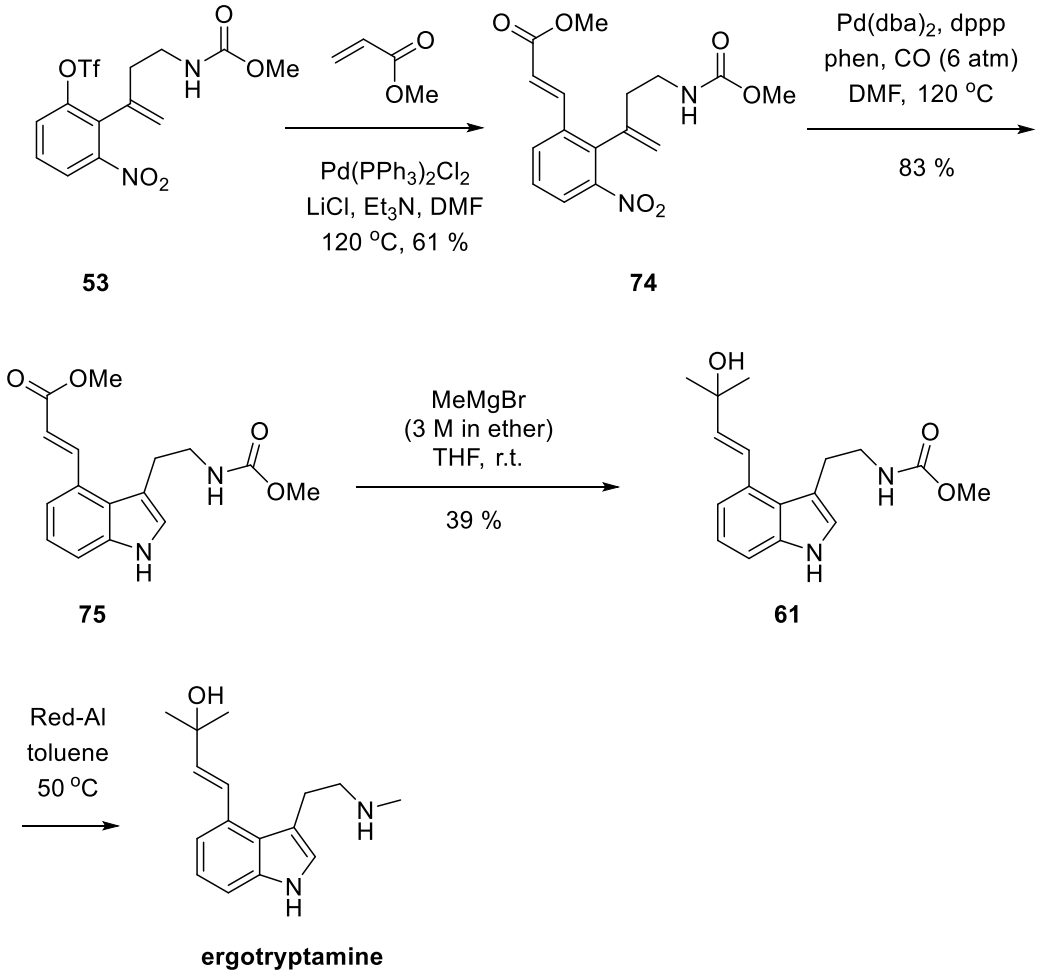
73 **aurantioclavine**

Entry	Conditions	Yield
1	TMSCl, NaI, CH_3CN, reflux, 2 h	not observed
2	TMSI, DCM, r.t., 2 h	not observed
3	NaOH (3.0 M, aq.), MeOH, reflux, 12 h	no reaction
4	KOH (3.0 M, aq.), 1-Propanol, reflux, 2 days	no reaction
5	MeLi (1.6 M in ether), THF, 0 ^oC, 4 h	not observed
6	$LiEt_3BH$ (1.0 M in THF, 3.0 eq.), THF, r.t., 3 days	no reaction
7	$LiEt_3BH$ (1.0 M in THF, 10.0 eq.), THF, 60 ^oC, 9 h	no reaction

In addition to auratioclavine, triflate **53** was thought to be the precursor of another natural product, ergotryptamine.[39] In three subsequent steps, triflate **53** was elaborated to indole **61** (scheme 42). First, Heck reaction of **53** with methyl acrylate gave 2-nitrostyrene **74** in 61% yield. Next, the N-heterocyclization of **74** resulted in the formation of indole **75** which was treated with methyl magnesium bromide in ether to afford indole **61**. Eventually, the Moc protecting group in **61** was smoothly reduced to N-methyl group

using Red-Al at 50 °C. The ^{1}H-NMR experiment of crude reaction mixture confirmed the formation of the desired ergotryptamine. However, the product was proved to be sensitive to purification by chromatography on silica gel. Other purification methods have been attempted, such as reversed phase chromatography, but no effective method has been developed to isolate pure ergotryptamine.

Scheme 42 Synthesis of ergotryptamine



53 **74** **75** **61** **ergotryptamine**

C. Conclusions

A concise total synthesis of aurantioclavine has been investigated starting from 2-iodo-3-nitrophenol. Key steps include a Kosugi-Migita-Stille coupling reaction, a Heck coupling reaction, a Lewis acid mediated intramolecular cyclization and an N-heterocyclization. The MOM group used in this synthesis as a protecting group successfully stabilized the phenol oxygen. The amine moiety was protected by a Moc group, however, no suitable condition for the Moc removal has been discovered. Meanwhile, the preparation of Heck precursor **45** and **53** utilizing selective Kosugi-Migita-Stille coupling has been studied, but none of the attempts succeeded. Moreover, natural products ergotryptamine and dehydrated ergotryptamine have been achieved from the building block **53**. Development of a feasible purification procedure is necessary to isolate ergotryptamine in the future. In general, this work provides a novel strategy for the synthesis of cycloclavine discussed in chapter 4 and other 3,4-fused indole alkaloids.

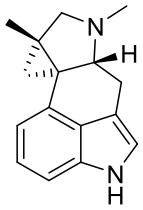
Chapter 4 Progress towards the synthesis of cycloclavine

A. Introduction

Cycloclavine is one of the clavine-type ergot alkaloids initially isolated from African morning glory seeds (*ipomoea hildebrandtii VATKE*) by Hofmann and co-workers in 1969.[40] To the best of our knowledge, cycloclavine is the only example of ergot alkaloid containing a fused pentacyclic framework (Figure 7). Recently, O'Connor and co-workers have reported a biosynthetic pathway to cycloclavine from a common intermediate chanoclavine-I via an enzyme catalyzed rearrangement process.[41] So far, cycloclavine has been synthesized by five research groups[42] however, no asymmetric synthesis has been reported.

Cycloclavine has three chiral centers at C-5, C-8 and C-10, a unique cyclopropane ring moiety, and a fused pentacyclic framework, which makes its synthesis very challenging, especially an asymmetric total synthesis.

Figure 7 Structure of cycloclavine



cycloclavine

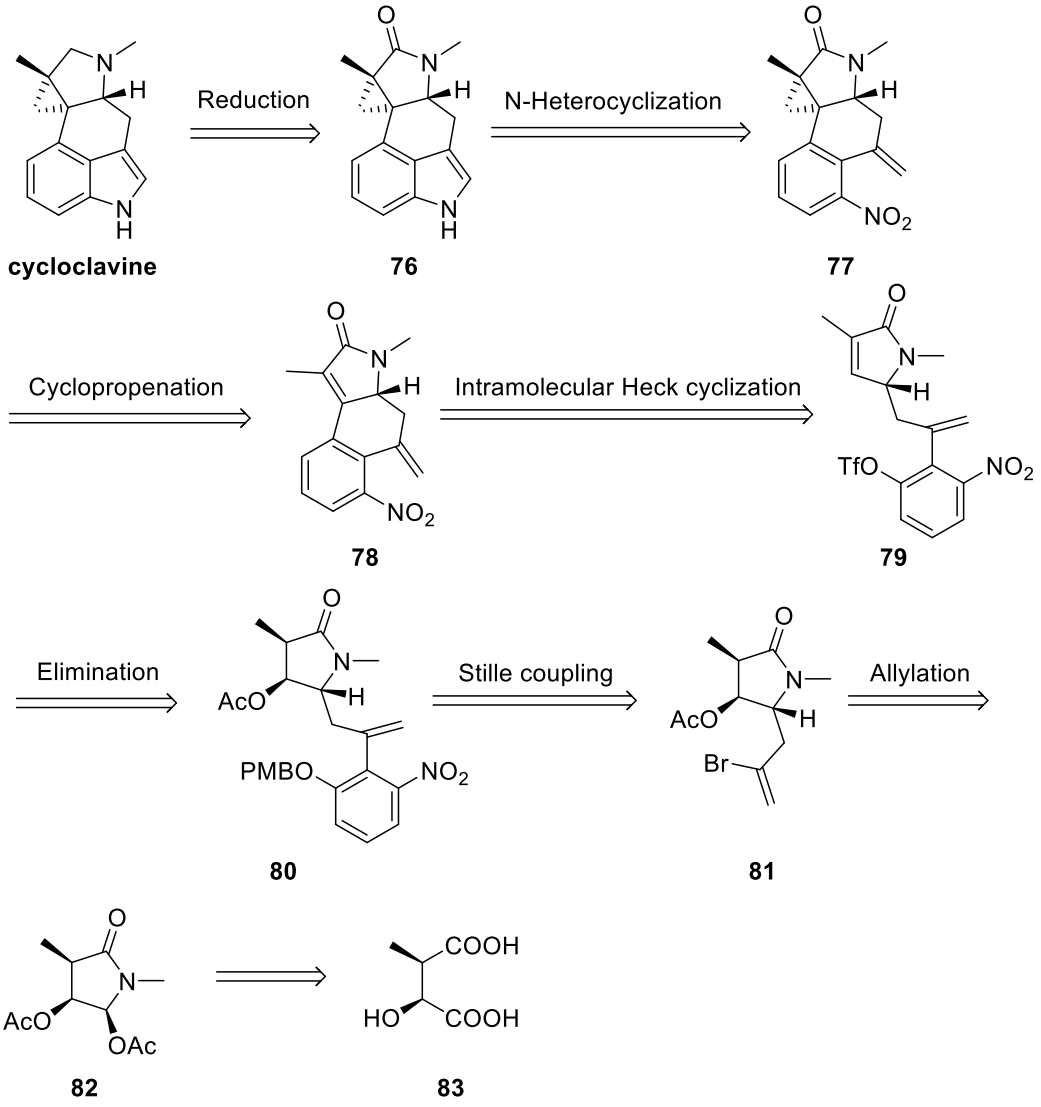
This chapter focus on the first asymmetric total synthesis of (+)-cycloclavine. We anticipated that the chirality at C-5 on cycloclavine could be achieved using the Lewis acid mediated allylation strategy applied in our previous syntheses[31]. Furthermore, the

pyrrolidine ring in cycloclavine could be produced following a similar synthetic route used in the synthesis of ht-13-A and ht-13-B. The indole core could be achieved in 2 steps including a Kosugi-Migita-Stille coupling and a N-heterocyclization in a late stage during the synthesis. A late formation of desired indole core will ensure a lower possibility of side reactions occurring in the early steps. Overall, the synthesis of cycloclavine is expected to be achieved via a short synthetic pathway based on our general strategy toward 3,4-fused indole alkaloids.

B. Results and Discussions

Based on our previous strategy for the synthesis of 3,4-fused indole alkaloid, retrosynthetic analysis of (-)-cycloclavine is described in Scheme 43. Cycloclavine could be prepared from a reduction of the carbonyl group in pyrrolidinone **76**. The indole core would be obtained from the carbon monoxide mediated N-heterocyclization of 2-nitrostyrene **77**. Installation of cyclopropane ring onto α,β-unsaturated amide **78** may furnished the tetracyclic intermediate **77**. The middle 6-membered ring in **78** may be obtained from an intramolecular Heck reaction of triflate **79**. The 1,5-dihydro-pyrrol-2-one ring in **79** may be achieved via a base promoted elimination reaction of **80**. In addition, deprotection of 4-methoxybenzyl group (PMB) followed by a reaction with Tf_2O should give the desired trifluoromethanesulfonate group in **79**. The benzene ring should be connected to the allyl side chain via a Kosugi-Migita-Stille coupling using the condition for the synthesis of **65** (Scheme 37). Compound **81** could be prepared from *N,O*-acetal **82** through a Lewis acid mediated allylation. Finally, compound **82** was thought to be prepared from known compound **83** via three-step procedure including a reported cyclization reaction,[43] a regioselective reduction, and an acetylation.

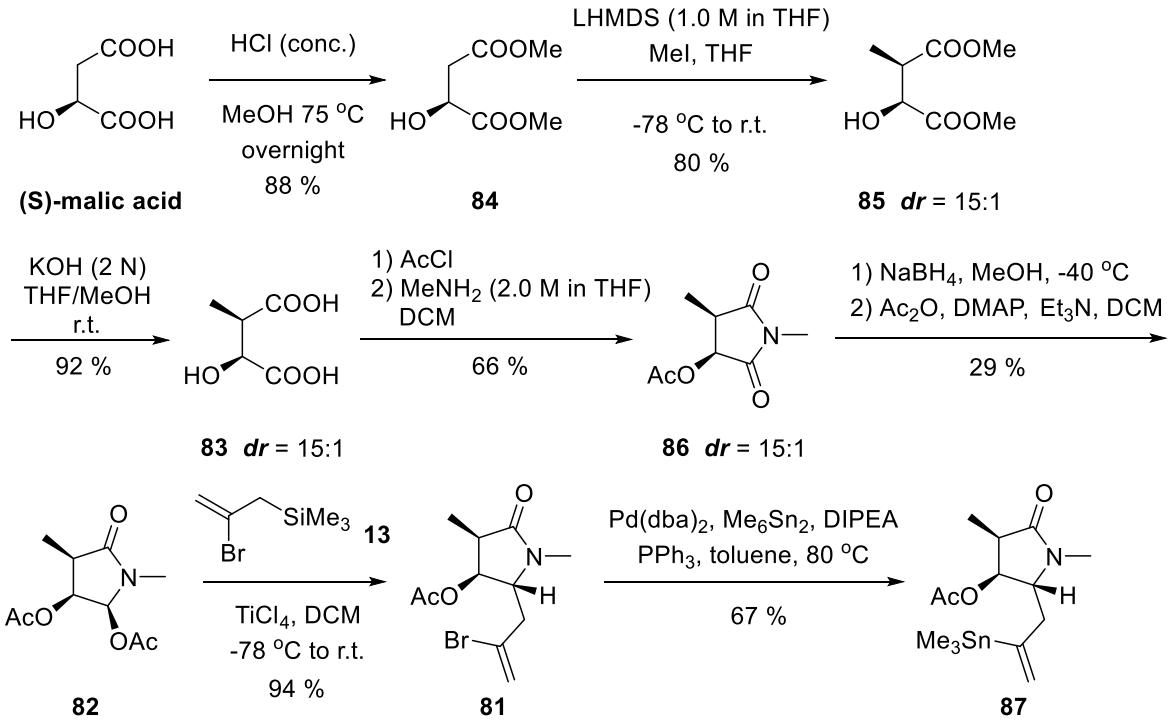
Scheme 43 Retrosynthetic analysis of cycloclavine



The synthesis began with the methylation of (S)-malic acid (Scheme 44). Treating (S)-malic acid in refluxing methanol with concentrated HCl afforded ester **84**. Compound **84** was then exposed to lithium bis(trimethylsilyl)amide in THF to generate an enolate intermediate which reacted with methyl iodide to give ester **85** as a 15:1 mixture of two inseparable diastereomers. In the next step, hydrolysis of **85** using potassium hydroxide in a mixture of THF and methanol gave methyl malic acid **83**, which was subsequently reacted with acetyl chloride and methylamine to form succinimide **86** with the same

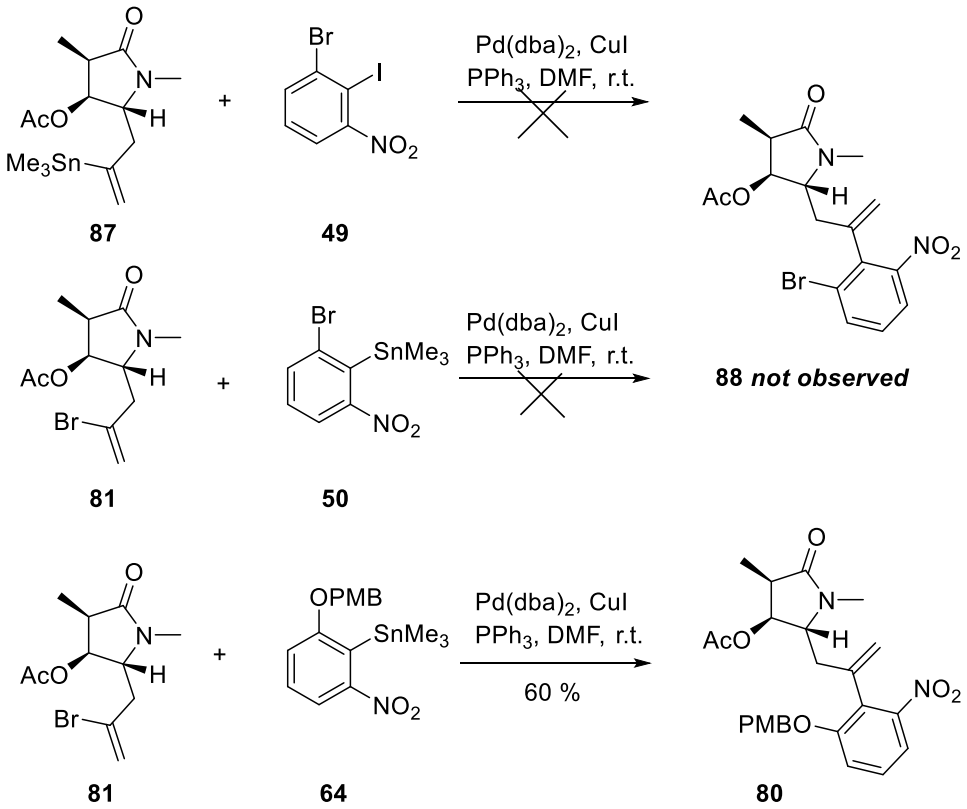
diastereomeric ratio as **85**. Gratifyingly, the regioselective reduction of **86** using sodium borohydride at -40 ^{o}C produced a *N,O*-hemiacetal intermediate as a single stereoisomer. Reduction of **86** at higher temperature (-20 ^{o}C to r.t.) resulted in a partial decomposition of the starting material as well as decreased diastereoselectivity. Acetylation of the remaining hydroxyl group was carried out to afford compound **82** in 42% yield (2 steps). The *N,O*-acetal moiety was activated by treating **82** with $TiCl_4$ leading to the formation of an acyliminium ion intermediate. After addition of 2-bromo-2-propen-1-yl trimethylsilane **13** to the reaction mixture, vinyl bromide **81** was formed as a single stereometric isomer in 94% yield. Replacement of the bromine in **81** by a trimethyltin group was readily achieved in the Pd(0)-hexamethylditin system giving trimethylstannane **87**. Both **81** and **87** can serve as starting materials for Kosugi-Migita-Stille coupling reaction in the next step.

Scheme 44 Synthesis of acetate **81** and trimethylstannane **87**



We next focused on the Kosugi-Migita-Stille coupling reaction to connect the desired benzene ring to the pyrrolidin-2-one species (Scheme 45). The first attempt was made by reacting trimethylstannane **87** with 2-iodo-3-bromo-nitrobenzene **49**, but target product **88** was not observed. Likewise, reaction between vinyl bromide **81** and trimethylstannane **50** gave no product. It is inferred that a steric hindrance problem might cause the failure of these two reactions. Nevertheless, compound **80** was successfully prepared by Kosugi-Migita-Stille coupling reaction of **81** and **64**.

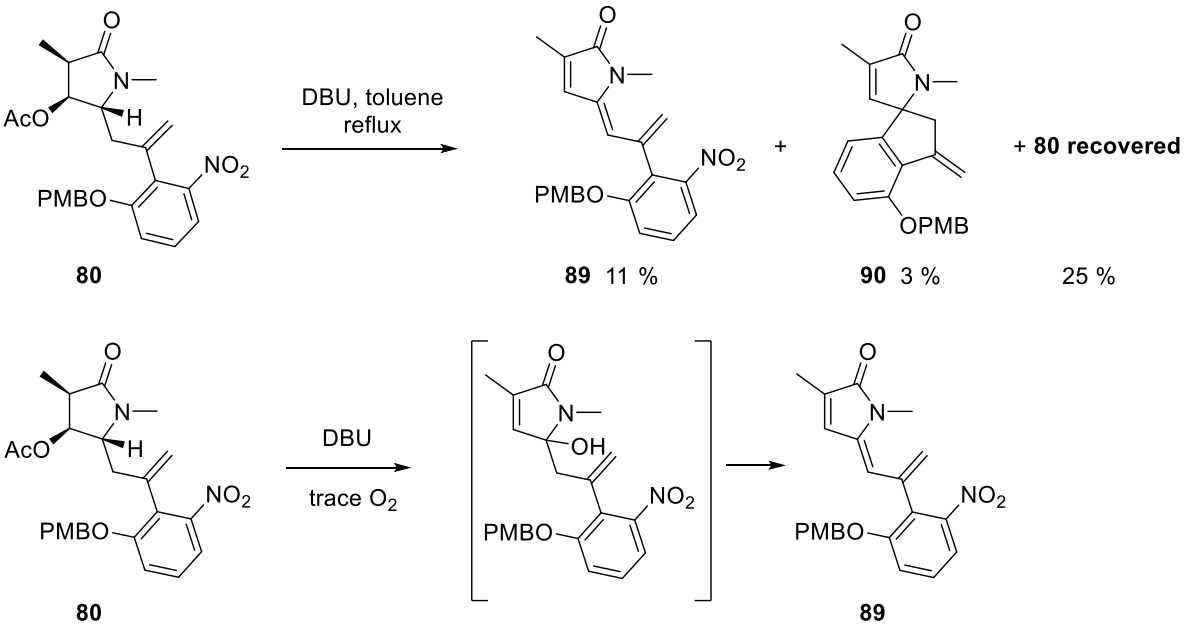
Scheme 45 Kosugi-Migita-Stille coupling toward **88** and **80**[a]



a. Preparations of compound **49**, **50** and **64** were discussed in chapter 3 (Scheme 31 and 36).

All attempted elimination reactions of **80** to build 1,5-dihydro-pyrrol-2-one moiety was unsuccessful and only two byproduct **89** and **90** were found (Scheme 46). A mechanism for this transformation was proposed. Treating compound **80** with 1,8-diazabicycloundec-7-ene (DBU) led to the formation of an enolate, which rapidly oxidized when trace O_2 remained in the system. Meanwhile, some of the enolates likely go through an intermolecular substitution reaction to afford spiro compound **90**. The oxidized intermediate underwent a dehydration process in the basic environment and eventually generated compound **89**. The elimination strategy used in this synthetic route resulted in a rapid deprotonation at C-5, which led to the formation of several byproducts and the loss of chirality.

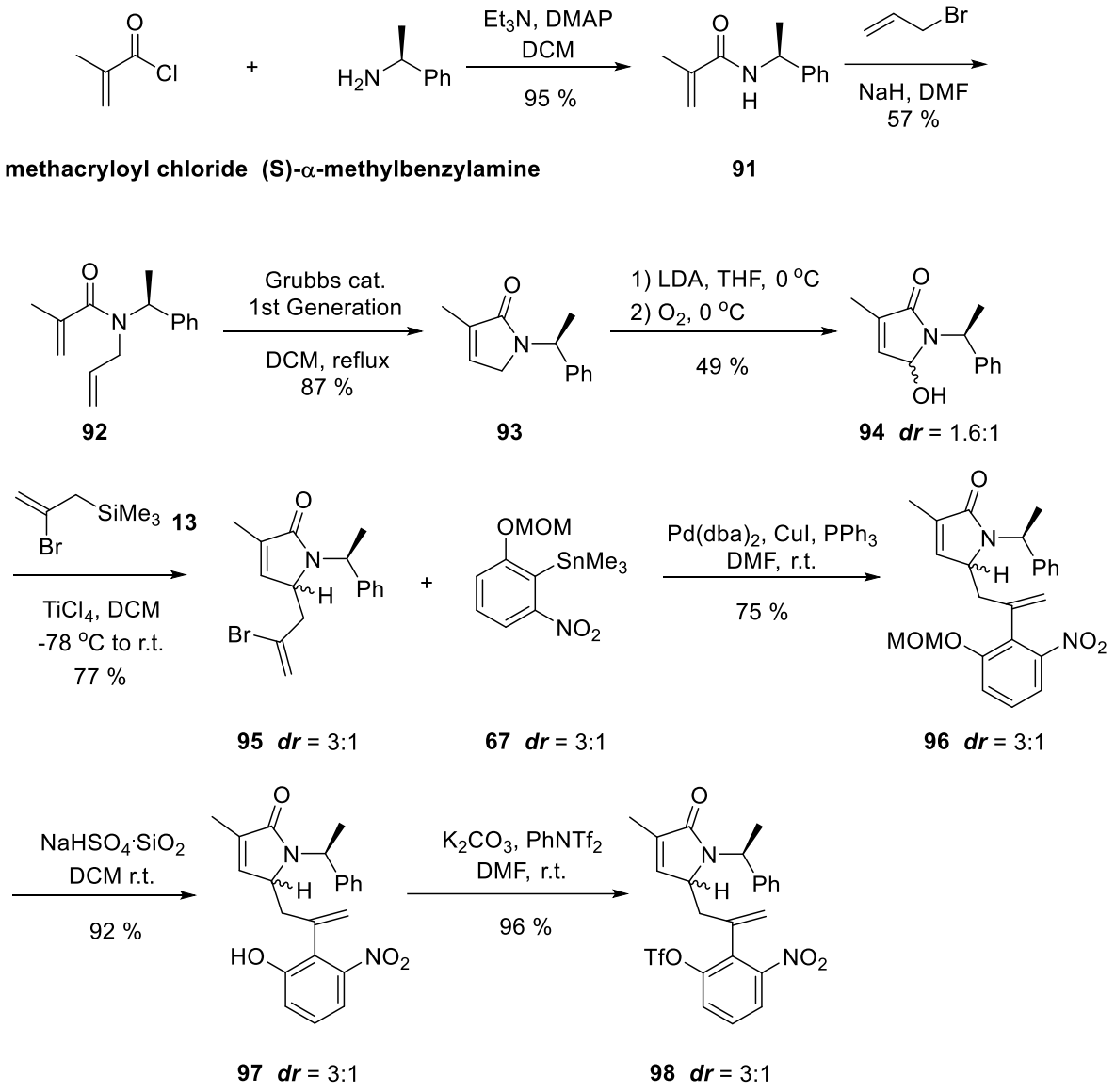
Scheme 46 Elimination of acetate **80**



Considering the unsuccessful elimination reaction in the previous synthetic route, an alternative pathway has been developed as described in Scheme 47. The synthesis

commenced with the preparation of amide **91** using commercially available methacryloyl chloride and (S)-α-methylbenzylamine. Allylation of **91** using sodium hydride and allyl bromide in DMF formed amide **92** which underwent ring closing metathesis with 1st generation Grubbs's catalyst to provide 1,5-dihydro-pyrrol-2-one **93**. Treatment of **93** with lithium diisopropylamide (LDA) in THF delivered the enolate intermediate. The latter was oxidized by O_2 to provide *N,O*-hemiacetal **94**. A high concentration of O_2 proved to be critical for the production of **94** in high yield. Following the allylation of **94** using $TiCl_4$ and 2-bromo-2-propen-1-yl trimethylsilane **13**, vinyl bromide **95** was obtained as a 3:1 mixture of two diastereomers. Compound **95** was converted into methoxymethyl phenyl ether **96** by Kosugi-Migita-Stille coupling. After attempts under several reaction conditions, we found that the MOM group could be slowly removed from **96** by a complex of sodium bisulfate and silica gel[44] forming phenol **97**. Finally, **97** was treated with potassium carbonate and N-phenyl-bis(trifluoromethanesulfonimide) to give triflate **98**.

Scheme 47 Synthesis of triflate **98**



C. Conclusions

The first asymmetric total synthesis of (+)-cycloclavine has been studied. The 1,5-dihydro-pyrrol-2-one core was achieved early in the synthesis via the ring closing metathesis strategy. The C-5 chiral center has been successfully installed utilizing a Lewis acid mediated allylation. Introduction of the benzene ring was achieved by a following Stille coupling reaction. Eventually, this synthesis fulfilled the production of triflate **98**, which is an important precursor of (+)-cycloclavine.

Future effort will be focused on the study of intramolecular Heck cyclization reaction and finally the accomplishment of (+)-cycloclavine synthesis.

Chapter 5 Experimental

A. General Procedures

All NMR spectra were recorded in $CDCl_3$ at 600 MHz (^{1}H NMR) and 150 MHz (^{13}C NMR, 1H-broadband decoupled) at ambient temperature unless otherwise stated. Chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. HRMS data were obtained via electrospray ionization (ESI) with an ion trap mass analyzer. THF was purified and dried via two consecutive columns composed of activated alumina and Q5 catalyst on a Glass Contours solvent purification system. Dichloromethane and toluene were purified and dried via two consecutive columns composed of activated alumina on a Glass Contours solvent purification system. Hexanes and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures are referenced the first time they are used in the Experimental Section; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure.

B. Experimental

3(R)-[(*tert*-Butyldimethylsilyl)oxy]-5(R)-methyl-2-(2-propen-1-yl)pyrrolidine (5)

A solution of **1**[11] (762 mg, 2.21 mmol) and allyltrimethylsilane (1.40 mL, 8.81 mmol) in CH_2Cl_2 (10 mL) was cooled to -78 ℃ and stirred for 15 min. $TiCl_4$ (490 μL, 4.46 mmol) dissolved in CH_2Cl_2 (5 mL) was slowly added via an addition funnel. The cold bath was removed after 5 min, and the mixture was stirred at ambient temperature for an additional 2 h. The reaction mixture was poured into a slurry of $Na_2CO_3 \cdot 10H_2O$ (6 g) in CH_2Cl_2 (7 mL).

After being stirred for 15 min, the mixture was dried ($MgSO_4$) and filtered, and the solvent was removed to afford the crude mixture of isomeric **5** (511 mg). The product decomposed upon purification, and **5** was thus used as such to prepare **6**.

Spectral data from the 5:1 mixture of isomers of **5**.

Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.09 (d, *J* = 17.4 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.20 (br s, 1H), 3.58 (dt, *J* = 14.4, 7.2 Hz, 1H), 3.13 (dt, *J* = 7.1, 3.4 Hz, 1H), 2.33 (pent, *J* = 6.6 Hz, 1H), 2.26 (pent, *J* = 7.2 Hz, 1H), 1.92 (dd, *J* = 12.6, 6.6 Hz, 1H), 1.49 (ddd, *J* = 13.2, 9.0, 4.8 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.0, 116.5, 73.9, 62.9, 51.3, 43.8, 33.7, 25.8, 22.1, 18.0, -4.4, -5.0.

Partial spectral data for the minor isomer of **5**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.87 (pent, *J* = 4.2 Hz, 1H), 3.37 (ddd, *J* = 15.0, 12.6, 6.0 Hz, 2H), 2.95 (dt, *J* = 7.6, 5.3 Hz, 1H), 2.14 (pent, *J* = 7.4 Hz, 1H), 1.75 (ddd, *J* = 13.2, 6.6, 3.6 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7, 116.9, 67.0, 52.3, 43.5, 38.3, 21.3, 18.0, -4.5, -4.7.

1-(*tert*-Butoxycarbonyl)-3(R)-[(*tert*-butyldimethylsilyl)oxy]-5(R)-methyl-2-(2-propen-1-yl)-pyrrolidine (6)

To a suspension of **5** (511 mg, 2.00 mmol) and CH_2Cl_2 (5 mL) was added trimethylamine (0.84 mL, 6.03 mmol). The solution was cooled to -20 ℃ followed by addition of di-*t*-butyl dicarbonate (475 mg, 2.18 mmol), and the reaction mixture was stirred for 20 h slowly reaching ambient temperature. The reaction mixture was washed with H_3PO_4 (aqueous, 1 M, 2x5 mL) and saturated $NaHCO_3$ (aqueous, 2x5 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvents were removed giving crude **6** (627 mg). The material was used

as such to prepare **7** and **8**. In a separate experiment on an 8.21 mmol scale of **5**, the crude product was purified by chromatography (hexanes/EtOAc, 1:1), affording a mixture of isomers used for characterization.

Spectral data from the mixture for the major isomer/rotamer of **6**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (pent, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 18.6 Hz, 1H), 4.95 (d, *J* = 9.6 Hz, 1H), 4.45-4.43 (m, 1H), 4.03-3.76 (m, 2H), 2.61-2.49 (m, 1H), 2.26-2.24 (m, 1H), 1.93-2.08 (m, 1H), 1.69-1.65 (m, 1H), 1.47 (s, 9H), 1.19 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Partial spectral data for minor isomer/rotamer of **6**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (pent, *J* = 8.6 Hz, 1H), 1.45 (s, 9H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

Spectral data for the mixture of both isomers of **6**: ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0, 146.7, 136.7, 136.5, 135.1, 116.9, 116.3, 85.1, 79.2, 78.9, 78.9, 70.8, 70.2, 67.2, 60.4, 60.1, 52.4, 51.7, 50.6, 50.4, 40.0, 39.0, 33.7, 32.3, 28.6, 28.5, 27.4, 25.8, 25.7, 22.3, 21.2, 18.1, 17.9, -4.9; IR (ATR) 2957, 2930, 1693, 1383 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{37}NNaO_3Si$ ($M+Na^+$) 378.2440, found 378.2440.

1-(*t*-Butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(R)-(2-propen-1-yl)pyrrolidine (7) and 1-(*t*-Butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(S)-(2-propen-1-yl)pyrrolidine (8)

To a 0 ℃ cold solution of **6** (626 mg, 1.76 mmol) in THF (10 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 3.8 mL). The reaction mixture was stirred for 26 h slowly allowing for the cold bath to reach ambient temperature. The reaction mixture was poured into H_2O (50 mL) and extracted with EtOAc (4x25 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. Purification by

chromatography (hexanes/EtOAc, 7:3) gave **7** (286 mg, 1.18 mmol, 54 %) followed by **8** (56 mg, 0.23 mmol, 11 %).[45]

Spectral data of **7** as a mixture of rotamers at ambient temperature: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.95-5.88 (m, 1H), 5.10 (d, *J* = 17.4 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.54 (s, 1H), 3.89 (br s, 2H), 2.91 (br s, 1H), 2.55 (s, 1H), 2.37 (s, 1H), 2.08-2.04 (m, 1H), 1.82-1.78 (m, 1H), 1.47 (s, 9H), 1.19 (br s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0, 136.3, 116.5, 79.3, 70.4, 70.1, 59.5, 50.5, 39.2, 38.2, 33.6, 32.3, 28.4, 21.8, 20.7; IR (ATR) 3436, 1663, 1366, 1172, 1063 cm^{-1}; $[\alpha]^{25}_{D}$ = -39.6 (*c* 1.02, $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{24}NO_3$ ($M+H^+$) 242.1756, found 242.1751.

Partial spectral data for **7** as a mixture of rotamers at 60 ℃: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.11 (dq, *J* = 17.4, 1.8 Hz, 1H), 5.02 (d with further fine splitting, *J* = 10.2 Hz, 1H), 4.51 (dt, *J* = 16.8, 7.2 Hz, 1H), 3.93 (br s, 1H), 3.87 (pent, *J* = 6.6 Hz, 1H), 2.54 (pent, *J* = 7.2 Hz, 1 Hz, 0.5H), 2.45 (br s, 1H), 2.21 (br s, 1H), 2.04 (ddt, *J* = 12.0, 10.8, 9.0 Hz, 1H), 1.79 (ddd, *J* = 12.0, 6.6, 1.8 Hz, 1H), 1.47 (s, 9H), 1.19 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.1, 136.5, 129.9, 116.5, 79.3, 70.6, 59.7, 50.7, 39.2, 33.0, 28.5, 28.4, 21.3.

Spectral data for **8** as a mixture of rotamers at ambient temperature: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.77-5.84 (m, 1H), 5.09-5.06 (m, 2H), 4.11 (s, 1H), 4.00 (br s, 1H), 3.78 (s, 1H), 2.42 (br s, 1H), 2.06-2.09 (m, 3H), 1.74-1.79 (m, 1H), 1.47 (s, 9H), 1.27 (br s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 134.8, 117.2, 79.3, 73.2, 66.8, 52.1, 40.6, 38.6, 28.5, 21.9; IR (ATR) 3405, 1664, 1390, 1169, 1096 cm^{-1}; $[\alpha]^{25}_{D}$ = -8.1 ± 0.7 (*c* 5.75, MeOH); HRMS (ESI) calcd for $C_{13}H_{24}NO_3$ ($M+H^+$) 242.1756, found 242.1751.

Partial spectral data for **8** as a mixture of rotamers at 60 ℃: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.8, 10.2, 6.9 Hz, 1H), 5.09-5.05 (m, 2H), 4.11 (t, *J* = 1.2 Hz, 1H), 4.00 (q, *J*

= 6.6 Hz, 1H), 3.76 (br s, 1H), 2.44-2.42 (m, 1H), 2.09 (dt with further fine splitting, *J* = 15.0, 7.8 Hz, 1H), 2.05 (dddd, *J* = 13.7, 7.4, 2.7, 1.3 Hz, 1H), 1.76 (ddd, *J* = 13.8, 8.4, 4.8 Hz, 1H), 1.73 (br s, 1H), 1.47 (s, 9H), 1.26 (d, *J* = 6.6 Hz, 3H); Ambient temperature: ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 134.9, 117.1, 79.3, 73.7, 67.0, 52.3, 40.8, 38.6, 28.6, 22.1.

2(R)-(2-Propen-1-yl)-1-(*t*-butoxycarbonyl)-3(S)-(2-bromo-3-nitrophenoxy-5(R)-methyl-pyrrolidine (10)

To a solution of **7** (423 mg, 1.75 mmol) in THF (5 mL) were added triphenylphosphine (690 mg, 2.63 mmol) and **9** (574 mg, 2.63 mmol). The solution was cooled to 0 ℃ in an ice bath, and diisopropylazodicarboxylate (520 μL, 2.62 mmol) was added dropwise. The mixture was stirred at ambient temperature for 2 h. The solvent was removed, and the resulting mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ (sat. aqueous, 25 mL) and HCl (10 % aqueous, 25 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed. Purification by chromatography (hexanes/EtOAc, 7:3) gave **10** (542 mg, 1.23 mmol, 70 %) as a pale yellow oil.

Spectral data for **10** as a mixture of rotamers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.8 Hz, 0.5H), 7.35 (t, *J* = 7.2 Hz, 0.5H), 7.30 (d, *J* = 9.0 Hz, 0.5H), 7.29 (d, *J* = 8.4 Hz, 0.5H), 7.05 (d, *J* = 8.4 Hz, 1H), 5.90-5.80 (m, 1H), 5.19 (d, *J* = 16.8 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 4.70 (s, 0.5H), 4.69 (s, 0.5H), 3.96-4.14 (m, 2H), 2.77 (d, *J* = 13.2 Hz, 0.5H), 2.62 (d, *J* = 9.6 Hz, 0.5H), 2.52-2.44 (m, 1H), 2.20-2.14 (m, 1H), 2.04-1.96 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 155.2, 153.8, 153.3, 152.2, 152.2, 134.3, 134.0, 128.4, 128.3, 118.7, 118.6, 116.6, 116.5, 116.1, 116.0, 105.5, 105.3, 82.4, 81.1, 79.6, 79.6, 62.9, 62.7, 60.3, 53.2, 53.1, 37.4, 36.4, 36.1, 35.5, 28.4, 21.7, 20.5; IR (ATR) 2976, 1682, 1534,

1387, 1269 cm^{-1}; $[\alpha]^{25}_D$ = 0.12 ± 0.01 (*c* 1.0, MeOH); HRMS (ESI) calcd for $C_{19}H_{26}BrN_2O_5$ ($M+H^+$) 441.1026, found 441.1023.

Tricyclic Compound 11

A solution of **10** (200 mg, 0.45 mmol), $Pd(OAc)_2$ (7.4 mg, 0.03 mmol), and tri(o-tolyl)phosphine (39 mg, 0.13 mmol) in triethylamine (7 mL) in a Teflon screw-capped ACEGlass pressure tube was stirred at 120 ℃ for 31 h. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 9:1) to give (47 mg, 0.13 mmol, 29 %) as a white solid.[46]

Spectral data for **11** as a 1:1 mixture of rotamers: mp 125-127 ℃; ^{1}H NMR (600 MHz, CDCl3) δ 7.63 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.28-7.24 (m, 2H), 6.08 (br s, 1H), 5.83 (br s, 0.5H), 5.73 (br s, 0.5H), 4.90 (br s, 1H), 3.80 (ddt, *J* = 16.8, 10.2, 7.2 Hz, 3H), 3.29 (dd, *J* = 12.6, 7.2 Hz, 1H), 2.57 (br s, 1H), 1.93 (dt, *J* = 12.6, 10.8 Hz, 1H), 1.48 (s, 9H), 1.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.8, 153.9, 149.9, 136.2, 134.3, 133.2, 128.4, 128.2, 127.7, 127.3, 126.8, 125.9, 120.6, 120.5, 87.3, 86.8, 80.0, 61.8, 56.4, 52.2, 51.6, 40.3, 37.4, 28.4, 26.4, 21.8, 20.1; IR (ATR) 1691,1528, 1154, 1031, 712 cm^{-1}; $[\alpha]^{25}_D$ = 159.0 ± 0.6 (*c* 1.0, MeOH); HRMS (ESI) calcd for $C_{19}H_{25}N_2O_5$ ($M+H^+$) 361.1758, found 361.1758.

2(R)-(2-Bromo-2-propen-1-yl)-3(R)-[(*tert*-butyldimethylsilyl)-oxy]-5(R)-methyl-pyrrolidine (14) and 5(R)-[(*tert*-Butyldimethylsilyl)oxy]-(4a)-hexahydro-3-methylene-7(R)-methyl-1H-pyrrolo[1,2-c][1,3]oxazin-1-one (15)

A solution of **1** (123 mg, 0.36 mmol) and 2-bromo-2-propen-1-yl trimethylsilane **(13)** (250 μL, 1.43 mmol) in CH_2Cl_2 (4 μL) was cooled to -78 ℃ and stirred for 15 min. A solution of $TiCl_4$ (74 μL, 0.67 mmol) in CH_2Cl_2 (1.5 mL) was added slowly. The cold bath was

removed after 5 min, and the mixture was stirred at ambient temperature for an additional 1 h. $Na_2CO_3 \cdot 10H_2O$ (1.2 g) was added slowly. After stirring for 30 min, the mixture was dried ($MgSO_4$) and filtered, and the solvent was removed. Purification by chromatography (hexanes/EtOAc, 1:1) gave, in order of elution, **15** (32 mg, 0.11 mmol, 30 %, ***dr*** = 1.8:1) as a pale brown oil and **14** (67 mg, 0.20 mmol, 56 %, ***dr*** approximately 9:1)[47] as a brown oil. Spectral data for the major isomer of **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, *J* = 1.2 Hz, 1H), 5.49 (d, *J* = 1.6 Hz, 1H), 4.58 (br s, 1H), 4.30 (br dt, 1H), 3.66 (dpent, *J* = 8.6, 6.7 Hz, 1H), 3.58 (dt, *J* = 6.7, 3.9 Hz, 1H), 2.69 (d, *J* = 6.7 Hz, 2H), 1.96 (ddd, *J* = 13.3, 7.0, 2.0 Hz, 1H), 1.60 (ddd, *J* = 13.3, 9.0, 4.3 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.3, 118.8, 73.4, 61.0, 51.7, 43.4, 40.9, 25.8, 21.4, 18.0, -4.4, -4.9; IR (ATR) 2956, 1701, 1125, 1051, 833, 773 cm^{-1}; $[\alpha]^{25}_D$ = -12 ± 2 (*c* 0.1, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{29}BrNOSi$ ($M+H^+$) 334.1202, found 334.1197. Spectral data from a 1:1 mixture of diastereomeric **15**: ^{1}H (600 MHz, $CDCl_3$) NMR δ 4.65-4.63 (br m, 2H), 4.24 (t, *J* = 1.8 Hz, 1H), 4.22 (t, *J* = 1.8 Hz, 1H), 4.17 (t, *J* = 3.0 Hz, 1H), 4.10 (dp, *J* = 6.8, 4.0 Hz, 1H), 4.06 (br dp, *J* = 5.2, 4.4 Hz, 1H), 3.96 (ddd, *J* = 14.4, 7.8, 6.6 Hz, 1H), 3.59 (ddd, *J* = 12.0, 4.2, 3.6 Hz, 1H), 3.27 (ddd, *J* = 11.4, 7.8, 3.0 Hz, 1H), 2.81 (dd, *J* = 13.8, 3.0 Hz, 1H), 2.51 (ddt, *J* = 13.5, 11.8, 1.8 Hz, 1H), 2.37 (dd, *J* = 13.2, 4.2 Hz, 1H), 2.16 (ddt, *J* = 13.8, 12.0, 1.8 Hz, 1H), 2.07 (dd, *J* = 13.2, 6.6 Hz, 1H), 1.95 (ddd, *J* = 19.2, 10.2, 8.4 Hz, 1H), 1.84 (dd, *J* = 12.6, 6.0 Hz, 1H), 1.57 (ddd, *J* = 13.8, 10.2, 3.6 Hz, 1H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 152.3, 150.4, 149.0, 92.9, 92.8, 74.4, 71.3, 60.6, 60.0, 53.2, 51.9, 41.8, 39.6, 31.7, 26.5, 25.6, 25.5, 20.8, 19.9, 17.9, 17.8, -4.6, -4.7, -4.9, -5.1; IR (ATR) 2930, 1721, 1251, 1057, 832 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{28}NO_3Si$ ($M+H^+$) 298.1838, found 298.1829.

2(R)-(2-Bromo-2-propen-1-yl)-3(R)-[(*tert*-butyldimethylsilyl)-oxy]-1-(*t*-butoxycarbonyl)-5(R)-methyl-pyrrolidine (16) and (15)

A solution of **1** (100 mg, 0.29 mmol) and 2-bromoallyltrimethylsilane **(13)** (200 μL, 1.16 mmol) in CH_2Cl_2 (2 mL) was cooled to -78 ℃ and stirred for 15 min. $BF_3 \cdot Et_2O$ (82 μL, 0.66 mmol) was added slowly. The mixture was stirred at -78 ℃ for 1 h and then slowly warmed to -30 ℃ in 1 h and stirred for additional 1.5 h. Then, the mixture was quenched by pouring it into $NaHCO_3$ (sat. aqueous, 10 mL) at -30 ℃. The mixture was warmed to ambient temperature and extracted with EtOAc (3x10 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. The resulting residue was purified by chromatography (hexanes/EtOAc, 60:1) to afford, in order of elution, **16** (54 mg, 0.12 mmol, 43 %, ***dr*** = 8:1) as a colorless oil and **15** (20 mg, 0.07 mmol, 23 %, ***dr*** = 1.1:1) as a brown oil.

Spectral data for major isomer/rotamer of **16**: ^{1}H NMR (400 MHz, $CDCl_3$, 65 ℃) δ 5.59 (d, *J* = 1.0 Hz, 1H), 5.39 (s, 1H), 4.46 (dt, *J* = 10.8, 6.8 Hz, 1H), 4.17-4.08 (m, 1H), 3.84 (pent, *J* = 6.6 Hz, 1H), 2.86 (dd, *J* = 15.1, 6.4 Hz, 1H), 2.67-2.53 (m, 1H), 2.10-2.0 (m, 1H), 1.66 (dd, *J* = 11.0, 6.6 Hz, 1H), 1.45 (s, 9H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

Partial spectral data for minor isomer/rotamer of **16**: ^{1}H NMR (400 MHz, $CDCl_3$, 65 ℃) δ 5.58 (s, 1H), 5.46 (d, *J* = 0.9 Hz, 1H), 4.31 (pent, *J* = 4.7 Hz, 1H), 3.41 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.7 (br d, 1H), 1.44 (s, 9H).

Spectral data for mixture of both isomers of **16**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 153.9, 132.0, 131.8, 118.9, 118.4, 118.2, 79.8, 79.3, 78.9, 70.6, 70.0, 66.2, 58.5, 58.3, 52.5, 51.7, 50.4, 50.1, 40.8, 39.5, 39.4, 38.6, 28.5, 25.8, 25.7, 25.6, 22.1, 21.0, 18.2, 17.9, 17.8, -4.7, -4.8, -4.8, -4.9, -4.9; IR (ATR) 2957,1694, 1384, 1068, 774 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{37}BrNO_3Si$ ($M+H^+$) 434.1726, found 434.1722.

2(R)-(2-Bromo-2-propen-1-yl)-3(R)-[(*tert*-butyldimethylsilyl)-oxy]-1-(methoxycarbonyl)-5(R)-methylpyrrolidine (17)

To a suspension of **14** (61 mg, 0.18 mmol) and CH_2Cl_2 (1.0 mL) was added triethylamine (73 μL, 0.52 mmol), followed by dropwise addition of methyl chloroformate (30 μL, 0.39 mmol). The reaction mixture was stirred at ambient temperature for 20 h then poured into brine (20 mL) and extracted with EtOAc (3x20 mL). The organic phases were combined, dried ($MgSO_4$), and filtered. The solvents were removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 40:1) to give **17** (29 mg, 0.074 mmol, 41 %, ***dr*** approximately 9:1) as a colorless oil.

Spectral data for **17** from the mixture of isomers. Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$, 65 ℃) δ 5.55 (s, 1H), 5.39 (s, 1H), 4.48 (dt, *J* = 11.4, 7.2 Hz, 1H), 4.19 (q, *J* = 6.0 Hz, 1H), 3.91 (pent, *J* = 6.6 Hz, 1H), 3.63 (s, 3H), 2.87 (dd, *J* = 15.0, 5.4 Hz, 1H), 2.53 (br s, 1H), 2.11-2.02 (q, *J* = 9.6 Hz, 1H), 1.70 (dd, *J* = 12.6, 6.6 Hz, 1H), 1.22 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H).

Partial spectral data for the minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$, 65 ℃) δ 4.35 (pent, *J* = 4.8 Hz, 1H), 4.00 (m, 1H), 3.67 (s, 3H).

From the mixture of isomers/rotamers at ambient temperature: ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 132.2, 118.5, 117.8, 70.1, 59.0, 58.2, 52.0, 51.4, 50.3, 41.3, 39.6, 39.4, 38.5, 25.8, 25.7, 21.9, 21.0, 18.1, -4.9, -4.9; IR (ATR) 2955,1702, 1371, 1079, 774 cm^{-1}; $[\alpha]^{25}_D$ = 2.4 ± 0.1 (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{30}BrNNaO_3Si$ ($M+Na^+$) 414.1076, found 414.1072.

Alternative synthesis of 17

A solution of **1** (687 mg, 1.99 mmol) and 2-bromoallyltrimethylsilane **(13)** (1.37 mL, 7.97 mmol) in CH_2Cl_2 (22 mL) was cooled to -78 ℃ and stirred for 15 min. $TiCl_4$ (410 μL, 3.74 mmol) in CH_2Cl_2 (8 mL) was added slowly. The cold bath was removed after 5 min, and the mixture was stirred at ambient temperature for an additional 1 h. $Na_2CO_3 \cdot 10H_2O$ (6.68 g) was added slowly. After stirring for 30 min, the mixture was dried ($MgSO_4$) and filtered, and the solvent was removed to give a light yellow residue (802 mg). The residue was dissolved in CH_2Cl_2 (6 mL), and triethylamine (960 μL, 6.92 mmol) was added followed by dropwise addition of methyl chloroformate (400 μL, 5.16 mmol). The reaction mixture was stirred at ambient temperature for 18 h. Brine (50 mL) was added, and the mixture was extracted with EtOAc (3x50 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. The resulting residue was purified by chromatography (hexanes/EtOAc, 40:1) to give **17** (426 mg, 1.09 mmol, 55 %, ***dr*** approximately 9:1) as a colorless oil.

2(R)-(2-Bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)-5(R)-methylpyrrolidine (18)

To a solution of **17** (191 mg, 0.49 mmol) in THF (4 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 0.93 mL). The reaction mixture was stirred at ambient temperature for 2 h. The resulting mixture was poured into H_2O (20 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. Purification by chromatography (hexanes/EtOAc, 3:1) gave **18** (112 mg, 0.40 mmol, 82 %)[48] as a white solid.

Spectral data for **18** as a mixture of rotamers: mp 65-66 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (s, 0.4H), 5.62 (s, 0.6H), 5.46 (s, 1H), 4.57 (m, 1H), 4.18 (td, *J* = 6.0, 4.2 Hz, 1H), 3.94 (s, 1H), 3.66 (s, 3H), 2.98 (s, 0.4H), 2.87 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.57 (s, 0.6H), 2.00-2.35 (br m, 2H), 1.84 (dd, *J* = 11.4, 5.4 Hz, 1H), 1.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer δ 155.2, 131.6, 118.0, 69.1, 57.8, 51.4, 50.3, 40.9, 37.4, 20.4; Partial ^{13}C NMR (150 MHz, $CDCl_3$) spectral data for minor rotamer δ 131.1, 118.6, 58.8, 51.9, 50.7, 39.0, 38.7, 21.3; IR (ATR) 3359, 2965, 1668, 1376, 1068, 734 cm^{-1}; $[\alpha]^{25}_D$ = -11.6 ± 0.1 (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{10}H_{16}BrNNaO_3$ ($M+Na^+$) 300.0211, found 300.0200.

3(S)-(2-Bromo-3-nitrophenoxy)-2(R)-(2-bromo-propen-1-yl)-1-(methoxycarbonyl)-5(R)-methylpyrrolidine (19)

To a solution of **18** (607 mg, 2.18 mmol) in THF (32 mL) were added triphenylphosphine (1.95 g, 7.45 mmol) and **9** (713 mg, 3.27 mmol). The solution was cooled to 0 ℃, and diisopropylazodicarboxylate (1.74 mL, 8.84 mmol) was added dropwise. The mixture was stirred at ambient temperature for 19 h; brine (50 mL) was added, and the mixture was extracted with EtOAc (3x50 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed at reduced pressure. Purification by chromatography (CH_2Cl_2/hexanes, 1:1, then CH_2Cl_2) gave **19** (693 mg, 1.45 mmol, 66 %) as a pale yellow oil.

Spectral data for **19** as a mixture of rotamers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (t, *J* = 8.2 Hz, 0.5H), 7.37 (t, *J* = 8.1 Hz, 0.5H), 7.32 (d, *J* = 7.0 Hz, 0.5H), 7.31 (d, *J* = 7.9 Hz, 0.5H), 7.11 (d, *J* = 8.2 Hz, 0.5H), 7.10 (d, *J* = 8.2 Hz, 0.5H), 5.73 (s, 0.5H), 5.71 (s, 0.5H), 5.61 (s, 1H), 4.88 (d, *J* = 4.7 Hz, 0.5H), 4.83 (d, *J* = 4.6 Hz, 0.5H), 4.40 (dd, *J* = 10.0, 2.3 Hz, 0.5H), 4.31 (dd, *J* = 9.9, 2.8 Hz, 0.5H), 4.16 (pd, *J* = 6.3, 2.3 Hz, 0.5H), 4.08 (d, *J* = 6.4 Hz, 0.5H),

3.72 (s, 1.5H), 3.71 (s, 1.5H), 3.19 (dd, *J* = 14.5, 2.8 Hz, 0.5H), 2.94 (dd, *J* = 14.3, 3.0 Hz, 0.5H), 2.56-2.39 (m, 2H), 2.08 (d, *J* = 14.2 Hz, 0.5H), 2.06 (d, *J* = 14.5 Hz, 0.5H), 1.54 (d, *J* = 6.4 Hz, 1.5H), 1.48 (d, *J* = 6.5 Hz, 1.5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.9, 154.8, 154.8, 154.3, 152.0, 152.0, 129.2, 129.2, 128.5, 128.5, 120.4, 120.4, 116.9, 116.8, 116.3, 116.3, 105.4, 105.3, 81.4, 80.4, 62.6, 61.5, 53.5, 53.0, 52.2, 52.1, 44.1, 42.4, 36.2, 35.3, 21.5, 20.4; IR (ATR) 2954, 1686, 1533, 1357, 1268, 732 cm^{-1}; $[\alpha]^{25}_D$ = -1.4 ± 0.1 (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{18}Br_2N_2NaO_5$ ($M+Na^+$) 498.9480, found 498.9462.

Tricyclic Compound 20

A solution of **19** (100 mg, 0.21 mmol), $Pd(dba)_2$ (30 mg, 0.05 mmol), triphenylphosphine (55 mg, 0.21 mmol), and hexamethylditin (105 mg, 0.32 mmol) in toluene (2 mL) was stirred at 140 ℃ for 3 h. The mixture was cooled to ambient temperature, diluted with EtOAc (4 mL), and washed with NH_4OH (10 % aqueous, 4x2 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 10:1) to give **20** (29 mg, 0.09 mmol, 44 %)[49] as a brown solid.

Spectral data for **20** as a mixture of rotamers:[50] mp 139-142 ℃; ^{1}H NMR (600 MHz, $CDCl_3$, 65 ℃) δ 7.35 (br s, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.08 (br s, 1H), 5.26 (br s, 1H), 4.94 (s, 1H), 3.91 (br m, 2H), 3.70 (s, 3H), 2.53 (dt, *J* = 12.6, 7.2 Hz, 1H), 2.31 (br s, 1H), 1.74 (dd, *J* = 15.6, 9.6 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 155.2, 155.1, 154.7, 151.7, 139.3, 138.7, 129.3, 128.8, 128.3, 124.0, 121.9, 120.7, 119.7, 118.9, 116.1, 85.3, 78.6, 62.1, 57.5, 52.7, 52.0, 51.3, 43.5, 42.4, 39.5, 38.3, 37.7, 21.6, 20.1; IR (ATR) 2955, 1695, 1527, 1251, 1071, 733 cm^{-1}; $[\alpha]^{25}_D$ = -240.9 ± 0.3 (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{18}N_2NaO_5$ ($M+Na^+$) 341.1113, found 341.1111.

(6aR,8R,9aS)-7-Methoxycarbonyl-6,6a,7,8,9,9a-hexahydro-8-methyl-H-pyrrolo[2′,3′:6,7]oxepino[4,3,2-cd]indole (21)

A solution of **20** (119 mg, 0.37 mmol), $Pd(dba)_2$ (12.9 mg, 0.02 mmol), 1,3-bis(diphenylphosphino)propane (9.23 mg, 0.02 mmol), and 1,10-phenanthroline (8.12 mg, 0.05 mmol) in anhydrous DMF (1.2 mL) in a Teflon screw-capped ACE-Glass pressure tube was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 ℃ for 37 h. The mixture was cooled to ambient temperature, diluted with EtOAc (10 mL), and washed with brine (2x10 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 4:1) to afford **21** (76 mg, 0.27 mmol, 71 %) as a white solid.

Spectral data for **21** from a mixture of rotamers: mp 190-193 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.99 (dd, *J* = 7.8, 0.6 Hz, 1H), 6.97 (br s, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 4.44 (apparent dt, *J* = 7.8, 1.8 Hz, 1H), 4.35 (br s, 0.5H), 4.02 (br pent, *J* = 4.6 Hz, 1H), 3.95 (dpent, *J* = 9.6, 6.6 Hz, 1H), partially overlapping 3.9 (br s, 0.5H), 3.75 (s, 3H), 2.64 (br s, 1H), 2.54 (br s, 1H), 2.01 (dt, *J* = 12.6, 9.6 Hz, 1H), 1.53 (br s, 1.5H), 1.43 (br s, 1.5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.2, 151.5, 138.6, 122.6, 120.8, 116.8, 109.7, 105.6, 104.3, 84.4, 63.4, 52.3, 51.9, 39.7, 31.4, 30.1, 21.5, 20.0; IR (ATR) 3323, 2925, 1676, 1074, 733 cm^{-1}; $[\alpha]^{25}_D$ = -286.5 ± 0.4 (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{19}N_2O_3$ ($M+H^+$) 287.1396, found 287.1391.

6,6a(R),7,8,9,9a(S)-Hexahydro-7,8(R)-dimethyl-H-pyrrolo-[2′,3′:6,7]oxepino[4,3,2-cd]indole (ht-13-B)

To a solution of **21** (116 mg, 0.41 mmol) in anhydrous toluene (40 mL) was added sodium bis(2-methoxyethoxy)aluminumhydride (in toluene ~3.5 M, 2.56 mL, 8.96 mmol) dropwise. The mixture was stirred at 110 ℃ for 5 h and then allowed to cool to ambient temperature. Brine (80 mL) was added, and the mixture was extracted with EtOAc (3x80 mL). The organic phases were combined, dried ($MgSO_4$), and filtered. The solvent was removed, and the resulting residue was purified by chromatography (EtOAc) to give ht-13-B (88 mg, 0.36 mmol, 88 %) as a white solid.

Spectral data for synthetic **ht-13-B**: mp 180-182 ℃; 1H NMR (600 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.98 (s, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.8 Hz 1H), 4.45 (ddd, *J* = 10.2, 6.0, 4.2 Hz, 1H), 3.45 (dpent, *J* = 6.6, 2.4 Hz, 1H), 3.37 (dd, *J* = 15.0, 4.2 Hz, 1H), 3.17 (ddd, *J* = 12.0, 6.0, 4.2 Hz, 1H), 2.73 (ddd, *J* = 14.4, 10.2, 7.8 Hz, 1H), 2.65 (ddd, *J* = 14.4, 12.0, 1.8 Hz, 1H), 2.45 (s, 3H), 1.87 (ddd, *J* = 13.8, 3.6, 2.4 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.0, 138.8, 122.7, 120.3, 117.0, 110.7, 106.0, 104.0, 86.1, 67.3, 57.9, 38.6, 35.0, 29.0, 14.2; IR (ATR) 3400, 3154, 2925, 1244, 1067, 733 cm^{-1}; $[\alpha]^{25}_D$ = -202.1 ± 0.1 (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{19}N_2O$ ($M+H^+$) 243.1497, found 243.1492.

3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methoxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (28)

Lithium triethylborohydride in THF (1.0 M in THF, 18.8 mL) was added to a solution of **27** (9.89 g, 31.33 mmol) in THF (125 mL) at -78 ℃. After 40 min, the reaction was quenched with H_2O (100 mL) and the mixture was allowed to warm to room temperature. The mixture

was extracted with EtOAc (3x100 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. The crude product was dissolved in THF (370 mL), methyl iodide (5.02 mL, 80.59 mmol) and NaH (60 %, 2.15 g, 53.75 mmol) were added, and the mixture was stirred at room temperature for 16 h. The reaction was quenched with H_2O (500 mL) and extracted with EtOAc (3x200 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 10:1) gave **28** (3.46 g, 10.43 mmol, 33 %) as a yellow oil. Spectral data for **28** as mixture of rotamers: ^{1}H NMR(400 MHz, $CDCl_3$) δ 4.88 (s, 0.5H), 4.76 (s, 0.5H), 4.10 (s, 0.5H), 4.09 (s, 0.5H), 3.54-3.64 (m, 0.5H), 3.43-3.54 (m, 0.5H), 3.38 (s, 1.5H), 3.37-3.38 (m, 0.5H), 3.34-3.35 (m, 0.5H), 3.33 (s, 1.5H), 1.98-2.13 (m, 1H), 1.70-1.80 (m, 1H), 1.48 (s, 9H), 0.91 (s, 2H), 0.86 (s, 7H), 0.09 (s, 1H), 0.07 (s, 2.5H), 0.06 (s, 2.5H). ^{13}C NMR(150 MHz, $CDCl_3$) δ 155.8, 155.2, 94.2, 94.1, 79.8, 79.6, 75.0, 74.2, 55.9, 55.4, 44.5, 43.9, 31.6, 30.8, 28.4, 28.3, 25.6, 25.6, 17.9, 17.9, -4.8, -4.9, -5.0; IR (ATR) 2930, 2858, 1703, 1386, 1364, 1080, 832, 773 cm^{-1};$[\alpha]^{25}_D$ = +1.0 ± 0.2 (*c* 1.0, MeOH); HRMS (ESI) calcd for $C_{16}H_{33}NNaO_4Si$ ($M+Na^+$) 354.2077, found 354.2080.

2-(2-Bromo-allyl)-3-(*tert*-butyl-dimethyl-silanyloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (29) and 5-(*tert*-Butyl-dimethyl-silanyloxy)-3-methylene-hexahydro-pyrrolo[1,2-c][1,3]oxazin-1-one (30)

A solution of **28** (100 mg, 0.30 mmol) and 2-bromoallyltrimethylsilane **(13)** (0.21 mL, 1.22 mmol) in CH_2Cl_2 (2 mL) was cooled to -78 ℃ under N_2 and stirred for 15 min. $BF_3{\cdot}OEt_2$ (48 %, 86 μL, 0.685 mmol) was added slowly. The mixture was stirred under N_2 for 1 h during which time the temperature raised to -60 °C. The reaction was quenched with saturated $NaHCO_3$ (aq. 8 mL) at -60 °C. Then the mixture was warmed to room temperature

and extracted with EtOAc (3x10 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 10:1) gave **29** (51 mg, 0.12 mmol, 40 %, ***dr*** = 6:1) as a colorless oil and (hexanes/EtOAc, 3:1) gave **30** (8.3 mg, 0.029 mmol, 10 %) as a white solid.

Spectral data for major isomer of **29**: ^{1}H NMR(400 MHz, $CDCl_3$, 65 ^{o}C) δ 5.60 (s, 1H), 5.41 (s, 1H), 4.34 (dd, *J* = 14.6, 6.6 Hz, 1H), 4.10 (q, *J* = 6.2 Hz, 1H), 3.31-3.46 (m, 3H), 2.84 (dd, *J* = 14.9, 5.9 Hz, 1H), 1.94-2.02 (m, 1H), 1.76-1.85 (m, 1H), 1.46 (s, 9H), 0.91 (s, 9H), 0.08 (s, 6H).

Spectral data for **29** as mixture of isomers: ^{13}C NMR (100 MHz, $CDCl_3$, 65 ^{o}C) δ 154.7, 131.8, 118.9, 118.8, 118.1, 118.0, 79.6, 79.0, 72.0, 58.7, 42.9, 40.3, 31.8, 28.5, 28.5, 25.9, 25.8, 25.8, 18.1, 18.0, 18.0, 17.9, -4.7, -4.7, -4.9, -4.9; IR (ATR) 2971, 1740, 1696, 1388, 1365, 1217, 1115, 834, 774 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{35}BrNO_3Si$ ($M+H^+$) 420.1570, found 420.1555.

Spectral data for **30**: mp 69-70 ^{o}C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 4.68 (s, 1H), 4.28-4.31 (m, 1H), 4.26 (t, *J* = 1.7 Hz, 1H), 3.60-3.70 (m, 1H), 3.50-3.60 (m, 2H), 2.48-2.58 (m, 1H), 2.42 (dd, *J* = 13.8, 4.1 Hz, 1H), 1.89-1.95 (m, 2H), 0.88 (s, 9H), 0.09 (s, 2H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 150.5, 93.2, 72.1, 59.8, 44.6, 32.6, 26.8, 25.6, 18.0, -4.7, -5.0; IR (ATR) 3457, 3017, 2971, 2929, 2857, 1737, 1664, 1417, 1354, 1217, 1099, 835, 777 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{26}NO_3Si$ ($M+H^+$) 284.1682, found 284.1668.

2-(2-Bromo-allyl)-3-(*tert*-butyl-dimethyl-silanyloxy)-pyrrolidine (31) and and 5-(*tert*-Butyl-dimethyl-silanyloxy)-3-methylene-hexahydro-pyrrolo[1,2-c][1,3]oxazin-1-one (30)

A solution of **28** (306 mg, 0.92 mmol) and 2-bromoallyltrimethylsilane **(13)** (0.64 mL, 3.69 mmol) in CH_2Cl_2 (10 mL) was cooled to -78 ℃ under N_2 and stirred for 15 min. $TiCl_4$ (0.2

mL, 1.85 mmol) in CH_2Cl_2 (4 mL) was added slowly. The cold bath was removed after 15 min and the mixture was stirred at ambient temperature for an additional 1 h. $Na_2CO_3 \cdot 10H_2O$ (3.1 g) was added slowly. After stirring for 15 min, the mixture was dried ($MgSO_4$), filtered, and the solvent was removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 3:1) gave **30** (24 mg, 0.085 mmol, 9 %, ***dr*** = 12:1) as a white solid and (MeOH/EtOAc, 1:10) gave **31** (148 mg, 0.46 mmol, 50 %) as a yellow solid.

Spectral data for **31**: ^{1}H NMR(400 MHz, $CDCl_3$) δ 5.82 (s, 1H), 5.62 (br s, 1H), 5.52 (d, *J* = 1.6 Hz, 1H), 4.26-4.32 (m, 1H), 3.37-3.47 (m, 1H), 3.29 (dd, *J* = 19.2, 8.4 Hz, 1H), 3.07-3.17 (m, 1H), 2.82 (dd, *J* = 15.1, 7.7 Hz, 1H), 2.74 (dd, *J* = 15.0, 5.7 Hz, 1H), 1.98-2.09 (m, 1H), 1.81-1.90 (m, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.6, 119.2, 72.6, 61.8, 43.3, 40.4, 35.0, 25.8, 18.0, -4.4, -4.9; IR (ATR) 2928, 2857, 1738, 1708, 1364, 834, 775 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{27}BrNOSi$ ($M+H^+$) 320.1045, found 320.1030.

3(R)-*tert*-Butyldimethylsilyloxy-1-(methoxycarbonyl)pyrrolidin-2-one (33)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 251 μL, 0.25 mmol) was added to a solution of 3(R)-hydroxypyrrolidin-2-one **(22)** (54 mg, 0.25 mmol) in THF (1.0 mL) at -78 ^oC. The mixture was stirred at -78 ^oC under an atmosphere of N_2 for 30 min. Methyl chloroformate (21 μL, 0.28 mmol) was added slowly. The mixture was allowed to warm to ambient temperature over 1.5 h, then quenched by H_2O (10 mL) and extracted with EtOAc (3x10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed. Purification by chromatography on silica gel (hexanes/EtOAc, 8:1) gave **33** (54 mg, 0.20 mmol, 79 %) as a white solid.

Spectral data for **33**: mp 66-66.5 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.33 (dd, *J* = 9.4, 7.9 Hz, 1H), 3.85 (s, 3H), 3.84 (ddd, *J* = 11.1, 8.7, 2.3 Hz, 1H), 3.52 (ddd, *J* = 10.9, 9.7, 6.8 Hz, 1H), 2.28-2.34 (m, 1H), 1.95 (dq, *J* = 12.6, 9.4 Hz, 1H), 0.89 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 151.4, 70.7, 52.6, 41.1, 27.6, 24.9, 17.4, -5.3, -6.0; IR (ATR) 2956, 2929, 2857, 1790, 1699, 1442, 1388, 1358, 1323, 1150, 1051, 1003, 905, 838, 778, 697 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{24}NO_4Si$ ($M+H^+$) 274.1475, found 274.1470; $[\alpha]^{25}_D$ = 51.9 ± 0.2 (*c* 1.0, $CHCl_3$).

3(R)-*tert*-Butyldimethylsilyloxy-2(R/S)-hydroxy-1-(methoxycarbonyl)pyrrolidine (34)

Lithium triethylborohydride (1.0 M in THF, 5.64 mL, 5.64 mmol) was added to a solution of **33** (1.29 g, 4.70 mmol) in THF (20 mL) at -78 ^{o}C. The mixture was stirred under N_2 for 30 min at -78 ^{o}C then quenched with H_2O (40 mL). The mixture was warmed to ambient temperature and extracted with EtOAc (3x30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed. Purification by chromatography on silica gel (hexanes/EtOAc, 5:1) gave **34** (1.06 g, 3.85 mmol, 82 %, ***dr*** = 7:1) as a yellow oil.

Spectral data for the major isomer/rotamer of **34**: ^{1}H NMR (600 MHz, $CDCl_3$, 65 ^{o}C) δ 5.19 (s, 1H), 4.18 (s, 1H), 3.75 (s, 3H), 3.50-3.58 (m, 2H), 2.11-2.19 (m, 1H), 1.75-1.81 (m, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

Spectral data from the mixture of both isomers of **34**: ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 155.2, 87.0, 86.4, 76.6, 75.7, 52.1, 44.0, 43.6, 31.2, 30.3, 25.4, 17.6, -5.2; IR (ATR) 3427, 2955, 2931, 2858, 1689, 1453, 1380, 1253, 1103, 1056, 831, 774 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{25}NNaO_4Si$ ($M+Na^+$) 298.1451, found 298.1447.

2(R/S)-(2-Bromo-2-propen-1-yl)-3(R)-*tert*-butyldimethylsilyloxy-1-(methoxycarbonyl)-pyrrolidine (32)

A solution of **34** (996 mg, 3.62 mmol) and 2-bromo-2-propen-1-yl trimethylsilane **(13)** (2.50 mL, 14.5 mmol) in CH_2Cl_2 (60 mL) was cooled to -78 ℃ and stirred for 15 min. $TiCl_4$ (800 μL, 7.30 mmol) was added slowly under a N_2 atmosphere. The cold bath was removed after 15 min, and the mixture was stirred at ambient temperature for an additional 1.5 h. $Na_2CO_3 \cdot 10H_2O$ (12.8 g) was added slowly. After stirring for 30 min, the mixture was dried ($MgSO_4$) and filtered. The solvents were removed and the crude product was purified by chromatography on silica gel (hexanes/EtOAc, 10:1) to give **32** (988 mg, 2.61 mmol, 72 %, ***dr*** = 6:1) as a colorless oil.

Spectral data for the major isomer/rotamer of **32** from the mixture: ^{1}H NMR (600 MHz, $CDCl_3$, 65 ºC) δ 5.49 (s, 1H), 5.32 (s, 1H), 4.28 (dt, *J* = 7.9, 6.4 Hz, 1H), 4.05 (q, *J* = 6.2 Hz, 1H), 3.56 (s, 3H), 3.28-3.40 (m, 2H), 2.74 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.55 (br s, 1H), 1.86-1.96 (m, 1H), 1.68-1.79 (m, 1H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, 65 ºC) δ 155.5, 131.5, 117.6, 71.7, 58.8, 51.6, 42.9, 40.0, 31.6, 25.6, 17.8, -5.0, -5.2.

Spectral data for the mixture of both isomers of **32**: IR (ATR) 2955, 2930, 2894, 2857, 1702, 1448, 1383, 1119, 833, 772 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{28}BrNNaO_3Si$ ($M+Na^+$) 400.0920, found 400.0919.

Alternative synthesis of 32

A solution of **28** (195 mg, 0.59 mmol) and 2-bromoallyltrimethylsilane **(13)** (455 mg, 2.36 mmol) in CH_2Cl_2 (6.5 mL) was cooled to -78 ℃ and stirred for 15 min. $TiCl_4$ (130 μL, 1.18 mmol) was added slowly. The cold bath was removed after 5 min, and the mixture was

stirred at ambient temperature for an additional 1 h. $Na_2CO_3 \cdot 10H_2O$ (2 g) was added slowly. After stirring for 30 min, the mixture was dried ($MgSO_4$) and filtered, and the solvent was removed to give a light yellow residue (210 mg). The residue was dissolved in CH_2Cl_2 (2 mL), and triethylamine (267 μL, 1.91 mmol) was added followed by dropwise addition of methyl chloroformate (110 μL, 1.38 mmol). The reaction mixture was stirred at ambient temperature for 4 h. Brine (10 mL) was added, and the mixture was extracted with EtOAc (3x10 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. The resulting residue was purified by chromatography (hexanes/EtOAc, 20:1) to give **32** (98 mg, 0.26 mmol, 44 %) as a colorless oil.

2(R)-(2-Bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)pyrrolidine (35) and 2(S)-(2-bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)pyrrolidine (36)

To a solution of **32** (928 mg, 2.45 mmol) in THF (22 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 4.63 mL, 4.63 mmol). The reaction mixture was stirred at ambient temperature for 1 h. The resulting mixture was poured into H_2O (50 mL) and extracted with EtOAc (3x30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed. Purification by chromatography on silica gel (hexanes/EtOAc, 4:1 followed by 2:1) gave, in order of elution, **35** (438 mg, 1.66 mmol, 68 %) and **36** (103 mg, 0.39 mmol, 16 %) both as colorless oils.

Spectral data for **35**: ^{1}H NMR (600 MHz, $CDCl_3$, 65 ^{o}C) δ 5.69 (s, 1H), 5.48 (d, *J* = 1.3 Hz, 1H), 4.43-4.50 (m, 1H), 4.07 (dt, *J* = 8.3, 5.4 Hz, 1H), 3.67 (s, 3H), 3.55 (ddd, *J* = 10.9, 8.2, 5.1 Hz, 1H), 3.44 (dt, *J* = 10.9, 7.5 Hz, 1H), 3.01 (br s, 1H), 2.82 (dd, *J* = 14.5, 8.3 Hz, 1H), 2.17 (br s, 1H), 1.95-2.05 (m, 1H), 1.88 (ddt, *J* = 12.7, 7.3, 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, 65 ^{o}C) δ 155.8, 131.0, 118.3, 70.8, 59.5, 51.9, 43.7, 39.6, 31.7;

IR (ATR) 3415, 2954, 2897, 1671, 1451, 1385, 1196, 1108, 1062, 887, 771 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}BrNO_3$ ($M+H^+$) 264.0235, found 264.0231; $[\alpha]^{25}_D$ = -28.4 ± 0.1 (*c* 1.0, $CHCl_3$).

Spectral data for **36**: ^1H NMR (600 MHz, $CDCl_3$, 60 ºC) δ 5.63 (s, 1H), 5.51-5.52 (m, 1H), 4.32 (d, *J* = 2.7 Hz, 1H), 4.03 (dd, *J* = 9.4, 4.2 Hz, 1H), 3.71 (s, 3H), 3.55-3.65 (m, 1H), 3.44-3.50 (m, 1H), 2.91 (br s, 1H), 2.34 (ddd, *J* = 14.8, 9.4, 0.6 Hz, 1H), 2.03-2.10 (m, 1H), 1.96 (br s, 1H), 1.90-1.94 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.8, 155.7, 129.7, 129.6, 119.2, 119.1, 74.1, 73.2, 65.4, 64.3, 52.4, 44.4, 44.4, 44.2, 43.4, 31.7, 31.0; IR (ATR) 3422, 2955, 1673, 1451, 1384, 1197, 1119, 1093, 985, 892, 772 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}BrNO_3$ ($M+H^+$) 264.0235, found 264.0231; $[\alpha]^{25}_D$ = 3.2 ± 0.1 (*c* 1.0, $CHCl_3$).

3(S)-(2-Bromo-3-nitrophenyl)-2(R)-(2-bromo-2-propen-1-yl)-1-(methoxycarbonyl)-pyrrolidine (37)

To a solution of **35** (422 mg, 1.60 mmol) in THF (25 mL) was added triphenylphosphine (1.46 g, 5.58 mmol) and 2-bromo-3-nitrophenol **(9)** (525 mg, 2.41 mmol). The solution was cooled to 0 ℃, and diisopropylazodicarboxylate (1.26 mL, 6.40 mmol) was added dropwise. The mixture was stirred at ambient temperature for 17 h, brine (50 mL) was added, and the resulting mixture was extracted with EtOAc (3x50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by chromatography on silica gel (CH_2Cl_2/hexanes, 1:1, then CH_2Cl_2) to give **37** (530 mg, 1.14 mmol, 71 %) as a pale yellow oil.

Spectral data for **37**: ^1H NMR (600 MHz, $CDCl_3$, 65 ºC) δ 7.39 (t, *J* = 8.2 Hz, 1H), 7.34 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.17 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.72 (s, 1H), 5.58 (d, *J* = 1.6 Hz,

1H), 4.93 (s, 1H), 4.26-4.35 (m, 1H), 3.69-3.79 (m, 1H), 3.72 (s, 3H), 3.57-3.64 (m, 1H), 3.01 (br s, 1H), 2.50 (dd, *J* = 14.6, 9.7 Hz, 1H), 2.22-2.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, 65 ^{o}C) δ 155.2, 154.8, 151.9, 128.9, 128.4, 120.0, 118.2, 117.4, 106.4, 81.7, 61.9, 52.2, 44.4, 43.8, 29.1; IR (ATR) 2955, 1693, 1533, 1449, 1386, 1357, 1270, 1196, 1121, 1010, 903, 773 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}Br_2N_2NaO_5$ ($M+Na^+$) 484.9324, found 484.9322; $[\alpha]^{25}_D$ = 30.6 ± 0.1 (*c* 1.0, $CHCl_3$);

2,3,3a(*S*),9,10,10a(*R*)-Hexahydro-1-(methoxycarbonyl)-8-nitro-1*H*-benzoxepino[3,2-*b*]pyrrole (38)

A solution of **37** (60 mg, 0.13 mmol), $Pd(dba)_2$ (15 mg, 0.026 mmol), triphenylphosphine (27 mg, 0.10 mmol), and hexamethylditin (51.5 mg, 0.16 mmol) in toluene (1.5 mL) was stirred at 120 ℃ for 12 h. The mixture was cooled to ambient temperature, the solvent was removed and the resulting residue was purified by chromatography on silica gel (hexanes/EtOAc, 6:1) to give **38** (16.5 mg, 0.054 mmol, 42 %) as a brown oil.

Spectral data for **38**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 0.5H), 7.16-7.30 (m, 2H), 6.96 (d, *J* = 7.1 Hz, 0.5H), 5.29 (s, 0.5H), 5.10-5.21 (m, 0.5H), 4.93-4.99 (m, 1H), 3.23-4.06 (m, 8H), 2.48 (t, *J* = 11.3 Hz, 0.5H), 2.18-2.32 (m, 1.5H), 1.95-2.13 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.1, 156.1, 155.3, 152.0, 151.8, 139.1, 138.6, 128.9, 128.8, 128.3, 123.9, 121.9, 121.5, 120.8, 119.9, 119.7, 118.9, 116.1, 86.8, 80.7, 80.3, 62.5, 57.0, 56.6, 52.4, 44.2, 44.0, 43.1, 42.4, 39.3, 38.8, 30.8, 30.6, 29.3; IR (ATR) 2956, 2893, 1697, 1526, 1446, 1386, 1357, 1249, 1191, 1137, 1072, 825 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_5$ $(M+H)^+$ 305.1137, found 305.1143; $[\alpha]^{25}_D$ = -173.9 ± 0.1 (*c* 1.0, $CHCl_3$);

6,6a(*R*),7,8,9,9a(*S*)-Hexahydro-7-(methoxycarbonyl)-4*H*-pyrrolo[2',3':6,7]oxepino-[4,3,2-*cd*]indole (39)

A solution of **38** (49 mg, 0.16 mmol), $Pd(dba)_2$ (5.6 mg, 0.0097 mmol), 1,3-bis(diphenylphosphino)propane (4.0 mg, 0.0096 mmol), and 1,10-phenanthroline (3.5 mg, 0.019 mmol) in anhydrous DMF (800 μL) in an ACE-Glass pressure tube with an attached pressure head was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction was stirred under CO (6 atm) at 120 ℃ for 72 h. The mixture was cooled to ambient temperature, diluted with EtOAc (5 mL), and washed with brine (2x5 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography on silica gel (hexanes/EtOAc, 2:1) to afford **39** (29 mg, 0.11 mmol, 66 %) as a white solid.

Spectral data for **39**: mp 262.5-263 ℃; ^{1}H NMR (600 MHz, $CDCl_3$, 65 ^{o}C) δ 8.05 (br s, 1H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.98 (s, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 4.54 (dt, *J* = 10.6, 6.8 Hz, 1H), 3.88-4.01 (m, 3H), 3.75 (s, 3H), 3.36 (dt, *J* = 12.2, 5.6 Hz, 1H), 2.61 (t, *J* = 13.2 Hz, 1H), 2.38-2.44 (m, 1H), 2.21-2.30 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, 65 ^{o}C) δ 155.6, 151.9, 139.1, 122.9, 120.7, 117.2, 110.1, 106.1, 104.4, 86.4, 62.5, 52.3, 44.2, 31.3, 31.2; IR (ATR) 3280, 1680, 1450, 1390, 1250, 1077, 769, 735 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_3$ ($M+H^+$) 273.1239, found 273.1238; $[\alpha]^{25}_D$ = -288.6 ± 0.2 (*c* 0.5, $CHCl_3$);

6,6a(*R*),7,8,9,9a(*S*)-Hexahydro-7-methyl-4*H*-pyrrolo[2',3':6,7]oxepino[4,3,2-*cd*]indole (ht-13-A)

To a solution of **39** (21 mg, 0.077 mmol) in anhydrous toluene (8.5 mL) was added sodium bis(2-methoxyethoxy)aluminumhydride (in toluene ~3.5 M, 500 μL, 1.75 mmol)

dropwise. The mixture was stirred at 110 ℃ for 5 h and then allowed to cool to ambient temperature. Brine (20 mL) was added, and the mixture was extracted with EtOAc (3x15 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed. The resulting residue was purified by chromatography on silica gel (EtOAc/MeOH, 9:1) to give **ht-13-A** (16.8 mg, 0.074 mmol, 95 %) as a white solid.

Spectral data for **ht-13-A**: mp 228-230 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.00 (br s, 1H), 6.99 (t, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 4.45 (ddd, *J* = 9.4, 6.1, 2.9 Hz, 1H), 3.42 (dd, *J*= 14.6, 3.4 Hz, 1H), 3.11 (t, *J* = 8.5 Hz, 1H), 2.62-2.68 (m, 1H), 2.52-2.62 (m, 2H), 2.46-2.52 (m, 1H), 2.43 (s, 3H), 2.05-2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 138.7, 122.8, 120.1, 117.1, 111.0, 106.1, 104.0, 86.7, 72.9, 55.6, 40.5, 30.8, 29.2; IR (ATR) 3063, 2833, 1620, 1515, 1457, 1343, 1294, 1240, 1065, 776, 733 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ ($M+H^+$) 229.1341, found 229.1336; $[\alpha]^{25}_D$ = -185.1 ± 0.4 (*c* 0.36, $CHCl_3$).

Trifluoro-methanesulfonic acid 2-bromo-6-nitro-phenyl ester (43)

Trifluoromethane-sulfonic anhydride (2.25 mL, 13.4 mmol) was added to a solution of 2-bromo-6-nitrophenol **(42)** (2.44 g, 11.17 mmol) and triethylamine (2.34 mL, 16.8 mmol) in CH_2Cl_2 (35 mL) at 0 ºC. The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with H_2O (100 mL) and extracted with EtOAc (3x60 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 10:1) gave **43** (3.84 g, 10.97 mmol, 98 %,) as a yellow oil.

Spectral data for **43**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.98 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.45 (t, *J* = 8.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.4, 139.2,

139.2, 129.5, 125.6, 121.5, 119.4, 118.7, 117.2, 115.1; IR (ATR) 1539, 1431, 1347, 1208, 1129, 886, 855, 750, 717 cm^{-1}; HRMS (ESI) calcd for $C_7H_3BrF_3NNaO_5S$ ($M+Na^+$) 371.8765, found 371.8765.

[3-(2-Bromo-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester (45)

A solution of **43** (930 mg, 2.66 mmol), **44** (822 mg, 2.82 mmol), $Pd(PPh_3)_2Cl_2$ (37.3 mg, 0.053 mmol) and lithium chloride (338 mg, 7.97 mmol) in DMF (14 mL) was stirred at 60 ^oC for 5 h. The reaction was diluted with H_2O (60 mL) and extracted with EtOAc (3x30 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 20:1) gave **42** (457 mg, 2.10 mmol, 79 %) as a yellow solid, then (hexanes/EtOAc, 4:1) gave **45** (139 mg, 0.42 mmol, 16 %) as a brown solid.

Spectral data for **45**: mp 53.5-54 ^oC; ^1H NMR (400 MHz, $CDCl_3$ 65 ^oC) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 5.34 (s, 1H), 5.04 (s, 1H), 4.88 (br s, 1H), 3.66 (s, 3H), 3.46 (q, *J* = 6.3 Hz, 2H), 2.59-2.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 150.2, 142.2, 137.5, 136.9, 129.0, 124.4, 122.8, 116.8, 52.0, 38.5, 35.3; IR (ATR) 3337, 1699, 1525, 1353, 1256, 914, 748, 711 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}BrN_2O_4$ ($M+H^+$) 329.0137, found 329.0137.

Alternative synthesis of 45

A solution of **50** (16 mg, 0.044 mmol), **51** (9.32 mg, 0.037 mmol), $Pd(dba)_2$ (1.05 mg, 0.0018 mmol), copper (I) iodide (5.22 mg, 0.027 mmol) and triphenylphosphine (1.92 mg, 0.0073 mmol) in DMF (0.65 mL) was stirred at room temperature for 16 h. The reaction was diluted with H_2O (10 mL) and extracted with EtOAc (3x10 mL), dried ($MgSO_4$) and the

solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 5:1) gave **45** (2.5 mg, 0.0076 mmol, 21 %) as a brown solid.

(2-Bromo-6-nitro-phenyl)-trimethyl-stannane (50)

$Pd(PPh_3)_2Cl_2$ (1.6 mg, 0.0023 mmol), hexamethylditin (37.5 mg 0.11 mmol) and triphenylphosphine (0.96 mg, 0.0037 mmol) were added to a solution of 1-bromo-2-iodo-3-nitrobenzene **(49)** (25 mg, 0.076 mmol) in toluene (0.5 mL) at room temperature. The mixture was stirred under N_2 at 105 ^oC for 16 h. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3x5 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 20:1) gave **50** (16 mg, 0.044 mmol, 58 %) as a brown oil.

Spectral data for **50**: ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 0.45 (s, 9H). δ ^{13}C NMR(150 MHz, $CDCl_3$) δ 157.1, 142.5, 137.1, 133.2, 130.3, 122.3, -3.8; IR (ATR) 2988, 2909, 1521, 1345, 1078, 773, 737, 714 cm^{-1}; HRMS (ESI) calcd for $C_8H_9BrNO_2Sn$ ($M\text{-}CH_3^+$) 349.8839, found 349.8838.

Trifluoro-methanesulfonic acid 2-iodo-3-nitro-phenyl ester (52)

Trifluoromethanesulfonic anhydride (0.075 mL, 0.45 mmol) was added to a solution of 2-iodo-3-nitrophenol (100 mg, 0.38 mmol) and triethylamine (0.058 mL, 0.42 mmol) in CH_2Cl_2 (1 mL) at 0 ^oC. The mixture was stirred for 1 h at 0 ^oC. The reaction was quenched with brine (10 mL) and extracted with EtOAc (3x10 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 5:1) gave **52** (143 mg, 0.36 mmol, 95 %) as a yellow oil.

Spectral data for **52**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.62 (t, *J* = 8.3 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 151.4, 130.8, 125.0, 124.2, 121.8, 119.6, 117.5, 115.4, 84.6; IR (ATR) 1535, 1425, 1211, 1131, 938, 838, 804, 733 cm^{-1}; HRMS (ESI) calcd for $C_7H_3F_3INNaO_5S$ ($M+Na^+$) 419.8626, found 419.8624.

(2-Benzyloxy-6-nitro-phenyl)-trimethyl-stannane (56)

$Pd(PPh_3)_2Cl_2$ (360 mg, 0.51 mmol), hexamethylditin (8.86 g, 27 mmol) and triphenylphosphine (223 mg, 0.85 mmol) were added to a solution of **55** (6.39 g, 18 mmol) in toluene (115 mL) at room temperature. The mixture was stirred under N_2 at 110 ºC for 14 h. The reaction was quenched with H_2O (200 mL) and extracted with EtOAc (3x100 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 80:1) gave **56** (5.64 g, 14.39 mmol, 80 %,) as a yellow solid.

Spectral data for **56**: mp 87-88 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.35-7.44 (m, 6H), 7.09 (d, *J* = 8.1 Hz, 1H), 5.11 (s, 2H), 0.29 (s, 9H); ^{13}C NMR(150 MHz, $CDCl_3$) δ 164.0, 156.0, 135.9, 130.4, 128.6, 128.3, 127.9, 127.8, 116.5, 115.4, 71.0, -5.6; IR (ATR) 3069, 3035, 2979, 2917, 1591, 1251, 1021, 738, 698 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}NNaO_3Sn$ ($M+Na^+$) 416.0285, found 416.0283.

[3-(2-Benzyloxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester (57)

A solution of **56** (2.0 g, 5.10 mmol), **51** (1.09 g, 4.27 mmol), $Pd(dba)_2$ (123 mg, 0.21 mmol), triphenylphosphine (218 mg, 0.83 mmol) and copper (I) iodide (600 mg, 3.15 mmol) in DMF (75 mL) was stirred at r.t. for 14 h. The reaction was diluted with H_2O (500 mL) and

extracted with EtOAc (3x200 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 5:1) gave **57** (1.21 g, 3.40 mmol, 79 %) as an orange oil.

Spectral data for **57**: ^{1}H NMR (400 MHz, $CDCl_3$, 65 ^{o}C) δ 7.23-7.39 (m, 7H), 7.12 (d, *J* = 7.7 Hz, 1H), 5.23 (s, 1H), 5.11 (s, 2H), 4.98 (s, 1H), 4.92 (br s, 1H), 3.59 (s, 3H), 3.33 (q, *J* = 6.3 Hz, 2H), 2.67 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 156.3, 150.5, 139.7, 135.6, 128.7, 128.6, 128.2, 127.1, 126.2, 116.9, 115.9, 115.8, 71.1, 51.8, 38.7, 36.3; IR (ATR) 3431, 2950, 1707, 1526, 1259, 1043, 801, 736, 697 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_5$ ($M+H^+$) 357.1450, found 357.1449.

[2-(4-Benzyloxy-1H-indol-3-yl)-ethyl]-carbamic acid methyl ester (58)

A solution of **57** (300 mg, 0.84 mmol), $Pd(dba)_2$ (29 mg, 0.050 mmol), 1,3-bis(diphenylphosphino)propane (21 mg, 0.051 mmol), and 1,10-phenanthroline (18 mg, 0.1 mmol) in anhydrous DMF (4 mL) in a Teflon screw-capped ACE-Glass pressure tube was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 ℃ for 24 h. The mixture was cooled to ambient temperature, diluted with EtOAc (15 mL), and washed with brine (2x30 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 2:1) to afford **58** (216 mg, 0.67 mmol, 79 %) as a white solid.

Spectral data for **58**: mp 97-98 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 65 ^{o}C) δ 8.25 (br s, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.40-7.47 (m, 2H), 7.35-7.40 (m, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.83 (s, 1H), 6.61 (d, *J* = 7.7 Hz, 1H), 5.21 (s, 2H), 4.71 (br s, 1H), 3.65 (s, 3H), 3.47 (q, *J* = 6.6 Hz, 2H), 3.08 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ

157.1, 153.4, 138.2, 137.1, 128.5, 127.9, 127.5, 122.6, 121.4, 117.2, 112.9, 104.9, 100.2, 69.8, 51.8, 42.5, 27.1; IR (ATR) 3412, 3319, 2944, 1698, 1505, 1251, 1071, 730 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_3$ ($M+H^+$) 325.1552, found 325.1549.

[2-(4-Hydroxy-1H-indol-3-yl)-ethyl]-carbamic acid methyl ester (59)

A solution of **58** (478 mg, 1.47 mmol) and Pd/C (10 % wt., 57.4 mg, 0.054 mmol) in MeOH (19 mL) in a Teflon screw-capped ACE-Glass pressure tube was saturated with hydrogen (4 cycles to 1.5 atm of H_2). The reaction mixture was stirred under H_2 (1.5 atm) at r.t. for 16 h. The solvent were removed on a rotary evaporator at water aspirator pressure. The mixture was diluted with EtOAc (20 mL), and washed with brine (2x20 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 2:1) to afford **59** (286 mg, 1.22 mmol, 83 %) as a pink solid.

Spectral data for **59**: mp 165-167 ^oC; ^1H NMR (400 MHz, d-DMSO) δ 10.58 (s, 1H), 9.28 (s, 1H), 7.10 (t, *J* = 5.2 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.79 (dd, *J* = 8.1, 7.2 Hz, 1H), 6.75 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.29 (dd, *J* = 7.2, 1.2 Hz, 1H), 3.50 (s, 3H), 3.24-3.31 (m, 2H), 2.92 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR(100 MHz, d-DMSO) δ 156.6, 151.7, 138.6, 121.7, 120.9, 116.5, 111.9, 102.9, 102.7, 51.0, 42.2, 26.8; IR (ATR) 3396, 2971, 1739, 1454, 1366, 1217, 1040, 737 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}N_2O_3$ ($M+H^+$) 235.1083, found 235.1083.

Trifluoro-methanesulfonic acid 3-(2-methoxycarbonylamino-ethyl)-1H-indol-4-yl ester (60)

Trifluoromethanesulfonic anhydride (0.423 mL, 2.51 mmol) was added to a solution of **59** (141 mg, 0.60 mmol) and triethylamine (1.7 mL, 12.20 mmol) in CH_3CN (17 mL) at 0 ^oC.

The mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with H_2O (50 mL) and extracted with EtOAc (3x30 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 1:1) and then recrystallization (CH_2Cl_2/hexanes, 2:1) gave **60** (120 mg, 0.33 mmol, 54 %,) as a yellow solid.

Spectral data for **60**: mp 105-106 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.95 (s, 1H), 4.88 (br s, 1H), 3.67 (s, 3H), 3.51 (q, *J* = 6.8 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 142.7, 139.1, 124.5, 121.9, 121.8, 119.7, 119.5, 117.5, 115.4, 111.8, 111.3, 110.9, 52.1, 41.8, 26.4; IR (ATR) 3341, 2971, 1711, 1413, 1217, 1136, 1001, 865, 735 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}F_3N_2O_5S$ ($M+H^+$) 367.0576, found 367.0581.

2-Iodo-1-(4-methoxy-benzyloxy)-3-nitro-benzene (63)

4-Methoxybenzyl chloride (1.04 mL, 7.67 mmol) was added to a solution of 2-iodo-3-nitrophenol (2.00 g, 7.55 mmol) and potassium carbonate (1.14 g, 8.25 mmol) in CH_3CN (40 mL). The mixture was stirred under N_2 at 80 ^oC for 17 h. The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (3x60 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 10:1) gave **63** (2.64 g, 6.85 mmol, 91 %,) as a yellow solid.

Spectral data for **63**: mp 123-124 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.26 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.13 (s, 2H), 3.81 (s, 3H). δ ^{13}C NMR(100 MHz, $CDCl_3$) δ 159.5, 158.8, 155.5, 129.8, 128.8, 127.4, 116.9, 115.2, 114.0, 80.8, 71.7, 55.2; IR (ATR) 3014, 2971, 1738, 1515, 1374, 1218, 1012, 734 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{12}INNaO_4$ ($M+Na^+$)

407.9709, found 407.9704.

[2-(4-Methoxy-benzyloxy)-6-nitro-phenyl]-trimethyl-stannane (64)

$Pd(PPh_3)_2Cl_2$ (79.3 mg, 0.11 mmol), hexamethylditin (1.94 g, 5.92 mmol) and triphenylphosphine (49 mg, 0.19 mmol) were added to a solution of **63** (1.52 g, 3.95 mmol) in toluene (33 mL) at room temperature. The mixture was stirred under N_2 at 110 ºC for 18 h. The reaction was quenched with H_2O (60 mL) and extracted with EtOAc (3x40 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 40:1) gave **64** (1.125 g, 2.67 mmol, 68 %) as a yellow solid.

Spectral data for **64**: mp 78.5-79 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.11 (dd, *J* = 8.2, 0.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.02 (s, 2H), 3.83 (s, 3H), 0.27 (s, 9H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 164.0, 159.6, 155.9, 130.4, 129.6, 127.9, 127.8, 116.4, 115.3, 113.9, 70.7, 55.2, -5.6; IR (ATR) 3355, 2930, 1666, 1612, 1512, 1247, 1017, 861, 741 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{21}NNaO_4Sn$ ($M+Na^+$) 446.0390, found 446.0385.

{3-[2-(4-Methoxy-benzyloxy)-6-nitro-phenyl]-but-3-enyl}-carbamic acid methyl ester (65)

A solution of **64** (3.3 g, 7.82 mmol), **51** (1.66 g, 6.51 mmol), $Pd(dba)_2$ (187 mg, 0.33 mmol), triphenylphosphine (341.6 mg, 1.30 mmol), and copper (I) iodide (930.4 mg, 4.89 mmol) in DMF (116.5 mL) was stirred at r.t. for 22 h. The reaction was diluted with H_2O (1 L) and extracted with EtOAc (3x300 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography

(hexanes/EtOAc, 10:1, then hexanes/EtOAc, 5:1) gave **65** (2.05 g, 5.31 mmol, 81 %) as a yellow solid.

Spectral data for **65**: mp 77-77.5 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$, 65 ^{o}C) δ 7.29-7.34 (m, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.13 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.21 (s, 1H), 5.03 (s, 2H), 4.96 (s, 1H), 4.89 (br s, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 3.31 (q, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, 65 ^{o}C) δ 160.0, 156.9, 156.8, 150.8, 140.0, 129.1, 128.6, 127.9, 126.8, 116.9, 116.3, 115.8, 114.4, 71.4, 55.3, 51.7, 39.1, 36.6; IR (ATR) 2933, 1706, 1514, 1247, 1029, 817, 741 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{22}N_2NaO_6$ ($M+Na^+$) 409.1376, found 409.1370.

2-Iodo-1-methoxymethoxy-3-nitro-benzene (66)

Chloromethyl methyl ether (8.68 mL, 114.28 mmol) was added to a solution of 2-iodo-3-nitrophenol (13.41 g, 50.60 mmol) and potassium carbonate (28 g, 202.59 mmol) in DMF (73 mL). The mixture was stirred under N_2 at room temperature for 1.5 h. The reaction was quenched with H_2O (300 mL) and extracted with Ether (3x150 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 20:1) gave **66** (12.55 g, 40.61 mmol, 80 %) as a yellow solid.

Spectral data for **66**: mp 64-64.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.7 Hz, 1H), 7.29 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.22 (dd, *J* = 8.2, 1.4 Hz, 1H), 5.28 (s, 2H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 155.3, 129.9, 117.7, 117.2, 95.2, 80.8, 56.6; IR (ATR) 2937, 1535, 1458, 1375, 1254, 1152, 1002, 895 cm^{-1}; HRMS (ESI) calcd for $C_8H_9INO_4$ ($M+H^+$) 309.9576, found 309.9574.

(2-Methoxymethoxy-6-nitro-phenyl)-trimethyl-stannane (67)

$Pd(PPh_3)_2Cl_2$ (402 mg, 0.57 mmol), hexamethylditin (9.38 g 28.63 mmol) and triphenylphosphine (235 mg, 0.90 mmol) were added to a solution of **66** (5.9 g, 19.09 mmol) in toluene (165 mL) at room temperature. The mixture was stirred under N_2 at 110 ^oC for 15 h. The reaction was quenched with H_2O (300 mL) and extracted with EtOAc (3x150 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 40:1) gave **67** (5.23 g, 15.12 mmol, 79 %) as a red oil.

Spectral data for **67**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 7.34 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.19 (s, 2H), 3.48 (s, 3H), 0.36 (s, 9H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 162.8, 155.6, 130.5, 128.0, 117.7, 117.4, 94.4, 56.2, -5.5; IR (ATR) 2976, 2907, 1522, 1345, 1242, 1148, 1008, 895, 739 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{14}NO_4Sn$ ($M\text{-}CH_3^+$) 331.9945, found 331.9942.

[3-(2-Methoxymethoxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester (68)

A solution of **67** (4.25 g, 12.30 mmol), **51** (2.61 g, 10.23 mmol), $Pd(dba)_2$ (353.8 mg, 0.62 mmol), triphenylphosphine (643 mg, 2.45 mmol), and copper (I) iodide (1.76 g, 9.24 mmol) in DMF (190 mL) was stirred at room temperature under N_2 for 24 h. The reaction was diluted with H_2O (1 L) and extracted with EtOAc (3x300 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (CH_2Cl_2 then hexanes/EtOAc, 2:1) gave **68** (2.50 g, 8.04 mmol, 79 %) as a yellow oil.

Spectral data for **68**: ^1H NMR (600 MHz, $CDCl_3$, 65 ^oC) δ 7.39 (t, *J* = 4.6 Hz, 1H), 7.32 (d, *J* = 4.6 Hz, 2H), 5.25 (s, 1H), 5.19 (s, 2H), 5.03 (br s, 1H), 4.98 (s, 1H), 3.65 (s, 3H), 3.47 (s,

3H), 3.38 (q, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 154.4, 149.8, 139.7, 128.2, 126.2, 117.6, 116.0, 115.7, 94.3, 55.8, 51.2, 38.5, 35.7; IR (ATR) 2955, 1708, 1526, 1252, 1152, 1006, 905, 727 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}N_2O_6$ ($M+H^+$) 311.1243, found 311.1240.

[3-(2-Hydroxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester (54)

HCl (conc., 8.2 mL) was added to a solution of **68** (2.53 g, 8.15 mmol) in MeOH (82 mL) at room temperature. The mixture was stirred at room temperature for 23 h. The reaction was neutralized with $NaHCO_3$ (aqueous, 100 mL) and extracted with EtOAc (3x100 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 4:1, then hexanes/EtOAc, 2:1) gave **54** (1.80 g, 6.76 mmol, 83 %) as a yellow solid.

Spectral data for **54**: mp 121-121.5 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$, 65 ^{o}C) δ 7.49 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.29 (t, *J* = 8.2 Hz, 1H), 7.20 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.06 (br s, 1H), 5.50 (s, 1H), 5.19 (s, 1H), 4.97 (br s, 1H), 3.68 (s, 3H), 3.35 (q, *J* = 6.2 Hz, 2H), 2.60 (t, *J* = 6.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, 65 ^{o}C) δ 157.9, 154.2, 149.2, 139.5, 128.7, 123.9, 121.0, 119.2, 116.1, 52.3, 39.6, 37.7; IR (ATR) 3411, 1688, 1521, 1449, 1360, 1267, 818, 737 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}N_2NaO_5$ ($M+Na^+$) 289.0800, found 289.0795.

Alternative synthesis of 54

A solution of 2-iodo-3-nitrophenol (72 mg, 0.27 mmol), **44** (100 mg, 0.34 mmol), $Pd(dba)_2$ (3.12 mg, 0.0054 mmol), butylated hydroxytoluene (3.0 mg, 0.014 mmol), triphenylphosphine (5.7 mg, 0.022 mmol), and copper (I) iodide (52.8 mg, 0.28 mmol) in dioxane (5 mL) was stirred at 110 ^{o}C under N_2 for 20 h. The reaction was diluted with H_2O

(10 mL) and extracted with EtOAc (3x10 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 3:1) gave **54** (16 mg, 0.06 mmol, 22 %) as a yellow solid.

Trifluoro-methanesulfonic acid 2-(3-methoxycarbonylamino-1-methylene-propyl)-3-nitro-phenyl ester (53)

Trifluoromethanesulfonic anhydride (0.41 mL, 2.44 mmol) was added to a solution of **54** (599 mg, 2.25 mmol) and triethylamine (1.03 mL, 7.39 mmol) in CH_3CN (10 mL) at 0 ^oC. The mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with H_2O (30 mL) and extracted with EtOAc (3x20 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 2:1) gave **53** (773 mg, 1.94 mmol, 86 %) as a yellow oil.

Spectral data for **53**: ^1H NMR (600 MHz, $CDCl_3$, 65 ^oC) δ 7.85 (dd, *J* = 6.5, 2.8 Hz, 1H), 7.52-7.56 (m, 2H), 5.47 (s, 1H), 5.19 (s, 1H), 4.89 (br s, 1H), 3.66 (s, 3H), 3.42 (q, *J* = 6.5 Hz, 2H), 2.66 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, 65 ^oC) δ 160.0, 150.6, 147.2, 137.1, 131.9, 129.4, 125.5, 123.7, 121.8, 120.1, 119.7, 117.5, 115.4, 51.9, 39.0, 36.3; IR (ATR) 3344, 1702, 1533, 1423, 1211, 1136, 947, 845 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{13}F_3N_2NaO_7S$ ($M+Na^+$) 421.0293, found 421.0288.

Alternative synthesis of 53

A solution of **52** (34 mg, 0.086 mmol), **44** (30 mg, 0.10 mmol), $Pd(PPh_3)_2Cl_2$ (3 mg, 0.0043 mmol), triphenylphosphine (2.25 mg, 0.0086 mmol), and copper (I) iodide (12.2 mg, 0.064 mmol) in DMF (1 mL) was stirred at room temperature under N_2 for 26 h. The reaction was diluted with H_2O (5 mL) and extracted with EtOAc (3x5 mL), dried ($MgSO_4$) and the

solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 5:1) gave **53** (7.5 mg, 0.019 mmol, 22 %) as a yellow oil.

{3-[2-(3-Hydroxy-3-methyl-but-1-enyl)-6-nitro-phenyl]-but-3-enyl}-carbamic acid methyl ester (69)

$Pd(PPh_3)_2Cl_2$ (272.6 mg, 0.39 mmol), triethylamine (1.22 mL, 8.75 mmol), lithium chloride (247 mg, 5.83 mmol) and 2-methyl-3-buten-2-ol (2.03 mL, 19.42 mmol) were added to a solution of **53** (773 mg, 1.94 mmol) in DMF (41 mL) at room temperature. The mixture was stirred under N_2 at 120 ^oC for 14 h. The reaction was quenched with H_2O (150 mL) and extracted with EtOAc (3x60 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 2:1) gave **69** (355 mg, 1.06 mmol, 55 %) as a brown oil.

Spectral data for **69**: ^1H NMR (600 MHz, $CDCl_3$, 65 ^oC) δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 16.0 Hz, 1H), 6.31 (d, *J* = 16.0 Hz, 1H), 5.31 (s, 1H), 5.03 (s, 1H), 4.93 (br s, 1H), 3.66 (s, 3H), 3.41 (br s, 2H), 2.61 (br s, 2H), 1.42 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.1, 149.9, 142.3, 141.8, 137.8, 135.2, 129.7, 127.8, 122.9, 122.1, 115.8, 70.8, 52.2, 38.8, 36.3, 30.0, 29.3; IR (ATR) 3429, 2975, 1698, 1525, 1359, 1265, 908, 658 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}N_2NaO_5$ ($M+Na^+$) 357.1426, found 357.1415.

{2-[4-(3-Methyl-buta-1,3-dienyl)-1H-indol-3-yl]-ethyl}-carbamic acid methyl ester (70)

A solution of **69** (153 mg, 0.46 mmol), $Pd(dba)_2$ (15.79 mg, 0.028 mmol), 1,3-bis(diphenylphosphino)propane (11.32 mg, 0.028 mmol) and 1,10-phenanthroline (9.9 mg, 0.055 mmol) in anhydrous DMF (1.5 mL) in a Teflon screw-capped ACE-Glass pressure

tube was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 ℃ for 24 h. The mixture was cooled to ambient temperature, diluted with EtOAc (10 mL), and washed with brine (2x10 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 2:1) to afford **70** (67 mg, 0.24 mmol, 52 %) as a yellow solid.

Spectral data for **70**: mp 129.5-130 ºC; ^{1}H NMR (600 MHz, $CDCl_3$, 65 ºC) δ 7.93 (br s, 1H), 7.11-7.22 (m, 3H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.91 (s, 1H), 6.75 (d, *J* = 15.8 Hz, 1H), 5.04 (s, 1H), 4.99 (s, 1H), 4.55 (br s, 1H), 3.56 (s, 3H), 3.43 (q, *J* = 6.3 Hz, 2H), 3.04 (t, *J* = 6.7 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.0, 142.2, 137.3, 133.2, 131.5, 127.0, 124.6, 123.3, 122.4, 117.1, 117.1, 113.3, 110.5, 52.0, 41.5, 28.1, 18.7; IR (ATR) 3387, 3295, 2943, 1695, 1521, 1342, 1254, 1234, 963, 745 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}N_2NaO_2$ ($M+Na^+$) 307.1422, found 307.1419.

Methyl-{2-[4-(3-methyl-buta-1,3-dienyl)-1H-indol-3-yl]-ethyl}-amine (dehydrated ergotryptamine)

To a solution of **70** (42 mg, 0.15 mmol) in anhydrous toluene (14 mL) was added sodium bis(2-methoxyethoxy)aluminumhydride (in toluene ~3.5 M, 0.94 mL, 3.29 mmol) dropwise. The mixture was stirred at 110 ℃ for 2 h and then allowed to cool to ambient temperature. Brine (30 mL) was added, and the mixture was extracted with EtOAc (5x20 mL). The organic phases were combined, dried ($MgSO_4$), and filtered. The solvent was removed, and the resulting residue was purified by chromatography (1 % Et_3N in EtOAc/MeOH, 5:1) to give **dehydrated ergotryptamine** (25.3 mg, 0.11 mmol, 71 %) as a yellow solid.

Spectral data for **dehydrated ergotryptamine**: mp 157.5-158 ºC; ^{1}H NMR (600 MHz,

$CDCl_3$) δ 8.04 (br s, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 15.8 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 2.1 Hz, 1H), 6.87 (d, *J* = 16.0 Hz, 1H), 5.13 (s, 1H), 5.08 (s, 1H), 3.14 (t, *J* = 6.9 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.44 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.3, 137.3, 132.8, 131.5, 127.3, 124.8, 123.2, 122.3, 116.9, 116.8, 114.3, 110.5, 52.2, 36.3, 28.1, 18.7; IR (ATR) 2935, 2851, 1608, 1450, 1343, 1103, 962, 737 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}N_2$ $(M+H^+)$ 241.1705, found 241.1699.

{3-[2-(3-Methyl-buta-1,3-dienyl)-6-nitro-phenyl]-but-3-enyl}-carbamic acid methyl ester (71)

Pyridinium p-toluenesulfonate (0.2 mg, 0.00081 mmol) was added to a solution of **69** (4.5 mg, 0.014 mmol) in $CHCl_3$ (0.8 mL) at room temperature. The mixture was stirred at 55 °C for 22 h then cooled to room temperature. The solvent was removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 3:1) gave **71** (3 mg, 0.0095 mmol, 70 %) as a colorless oil.

Spectral data for **71**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.65 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.38 (td, *J* = 8.0, 0.5 Hz, 1H), 6.83 (d, *J*= 16.1 Hz, 1H), 6.59 (d, *J*= 16.1 Hz, 1H), 5.35 (s, 1H), 5.18 (s, 1H), 5.16 (s, 1H), 5.04 (s, 1H), 4.95 (br s, 1H), 3.66 (s, 3H), 3.32-3.53 (m, 2H), 2.49-2.69 (m, 2H), 1.94 (s, 3H).

5-Methylene-1-(2-methyl-propenyl)-6-nitro-1,3,4,5-tetrahydro-benzo[c]azepine-2-carboxylic acid methyl ester (72)

$BF_3{\cdot}OEt_2$ (48 % BF_3, 0.024 mL) was added to a solution of **69** (30 mg, 0.0897 mmol) in diethyl ether (3 mL) at -78 °C under N_2. The mixture was stirred for 1.5 h at -78 °C then warmed to room temperature and stirred for 1 h. Additional $BF_3{\cdot}OEt_2$ (48 % BF_3, 0.01 mL)

was added and the mixture was stirred for additional 0.5 h at room temperature. The reaction was quenched with $Na_2CO_3 \cdot 10H_2O$ and dried ($MgSO_4$). The mixture was filtered and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 10:1) gave **72** (16 mg, 0.051 mmol, 56 %) as a yellow solid.

Spectral data for major rotamer of **72**: ^{1}H NMR (600 MHz, d-DMSO, 75 ^{o}C) δ 7.67 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.49 (d, *J* = 7.1 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 5.88 (d, *J* = 6.2 Hz, 1H), 5.50 (d, *J* = 8.2 Hz, 1H), 5.27 (s, 1H), 4.94 (s, 1H), 3.86-3.96 (m, 1H), 3.60 (s, 3H), 3.40 (ddd, *J* = 14.3, 10.7, 3.9 Hz, 1H), 2.61 (td, *J* = 13.1, 3.8 Hz, 1H), 2.50-2.55 (m, 1H), 1.75 (s, 3H), 1.69 (s, 3H).

Spectral data for **72** as mixture of rotamers: mp 94-94.5 ^{o}C; ^{13}C NMR (150 MHz, $CDCl_3$, 65 ^{o}C) δ 156.0, 151.4, 143.5, 142.0, 138.3, 135.0, 131.7, 127.5, 121.9, 121.3, 117.9, 59.1, 52.7, 52.6, 43.5, 37.1, 25.6, 25.6, 18.3; IR (ATR) 2956, 1694, 1528, 1439, 1364, 1247, 912, 729 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_4$ ($M+H^+$) 317.1501, found 317.1498.

6-(2-Methyl-propenyl)-3,4-dihydro-1H,6H-azepino[5,4,3-cd]indole-5-carboxylic acid methyl ester (73)

A solution of **72** (203 mg, 0.64 mmol), $Pd(dba)_2$ (22 mg, 0.038 mmol), 1,3-bis(diphenylphosphino)propane (15.87 mg, 0.039 mmol), and 1,10-phenanthroline (13.84 mg, 0.077 mmol) in anhydrous DMF (3.5 mL) in a Teflon screw-capped ACE-Glass pressure tube was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 ℃ for 24 h. The mixture was cooled to ambient temperature, diluted with EtOAc (20 mL), and washed with brine (2x20 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue

was purified by chromatography (hexanes/EtOAc, 2:1) to afford **73** (138 mg, 0.49 mmol, 76 %) as a yellow solid.

Spectral data for **73** as mixture of rotamers: mp 180.5-181 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (s, 0.5H), 8.09 (s, 0.5H), 7.22 (d, *J* = 8.1 Hz, 0.5H), 7.19 (d, *J* = 8.0 Hz, 0.5H), 7.11 (t, *J* = 7.4 Hz, 0.5H), 7.10 (t, *J* = 7.5 Hz, 0.5H), 7.00 (s, 0.5H), 6.98 (s, 0.5H), 6.87 (d, *J* = 7.3 Hz, 0.5H), 6.82 (d, *J* = 7.3 Hz, 0.5H), 6.56 (d, *J* = 8.2 Hz, 0.5H), 6.36 (d, *J* = 8.0 Hz, 0.5H), 5.37 (d, *J* = 8.6 Hz, 0.5H), 5.36 (d, *J* = 8.2 Hz, 0.5H), 4.08 (td, *J* = 13.9, 3.1 Hz, 0.5H), 3.95 (td, *J* = 14.1, 3.1 Hz, 0.5H), 3.73 (s, 1.5H), 3.71 (s, 1.5H), 3.50-3.60 (m, 1H), 3.30-3.38 (m, 0.5H), 3.19-3.27 (m, 0.5H), 3.01-3.04 (m, 0.5H), 2.98-3.01 (m, 0.5H), 1.89 (s, 1.5H), 1.84 (s, 1.5H), 1.72 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 155.8, 137.3, 137.2, 137.0, 136.0, 135.7, 125.2, 124.2, 124.1, 121.9, 121.7, 121.4, 121.0, 118.3, 117.7, 114.7, 114.4, 109.3, 109.1, 58.2, 58.1, 52.6, 52.5, 43.1, 42.8, 27.5, 26.6, 25.7, 25.7, 18.7, 18.4; IR (ATR) 3324, 2956, 1676, 1439, 1406, 1319, 913, 746, 730 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}N_2NaO_2$ ($M+Na^+$) 307.1422, found 307.1418.

3-[2-(3-Methoxycarbonylamino-1-methylene-propyl)-3-nitro-phenyl]-acrylic acid methyl ester (74)

$Pd(PPh_3)_2Cl_2$ (90 mg, 0.13 mmol), triethylamine (0.40 mL, 2.89 mmol), lithium chloride (81.5 mg, 1.92 mmol) and methyl acrylate (0.57 mL, 6.37 mmol) were added to a solution of **53** (255 mg, 0.64 mmol) in DMF (13.5 mL) at room temperature. The mixture was stirred under N_2 at 120 ^{o}C for 12 h. The reaction was quenched with H_2O (80 mL) and extracted with EtOAc (3x30 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 4:1) gave **74** (130 mg, 0.39 mmol, 61 %) as a brown oil.

Spectral data for **74**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79-7.83 (m, 2H), 7.77 (d, *J* = 16.1 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 5.42 (s, 1H), 5.06 (s, 1H), 5.03 (br s, 1H), 3.82 (s, 3H), 3.66 (s, 3H), 3.42 (q, *J* = 6.1 Hz, 2H), 2.58-2.67 (m, 1H), 2.49-2.58 (m, 1H); ^{13}C NMR(150 MHz, $CDCl_3$) δ 166.5, 160.0, 149.9, 140.8, 140.4, 137.0, 135.0, 130.4, 128.3, 124.9, 121.8, 117.9, 52.1, 52.0, 38.5, 37.3; IR (ATR) 3343, 2952, 1709, 1527, 1318, 1245, 1174, 752 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}N_2NaO_6$ ($M+Na^+$) 357.1063, found 357.1058.

3-[3-(2-Methoxycarbonylamino-ethyl)-1H-indol-4-yl]-acrylic acid methyl ester (75)

A solution of **74** (121 mg, 0.36 mmol), $Pd(dba)_2$ (12.46 mg, 0.022 mmol), 1,3-bis(diphenylphosphino)propane (8.95 mg, 0.022 mmol), and 1,10-phenanthroline (7.82 mg, 0.043 mmol) in anhydrous DMF (1.4 mL) in a Teflon screw-capped ACE-Glass pressure tube was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 ℃ for 28 h. The mixture was cooled to ambient temperature, diluted with EtOAc (10 mL), and washed with brine (2x10 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 2:1) to afford **75** (91 mg, 0.30 mmol, 83 %) as a yellow oil.

Spectral data for **75**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 8.43 (d, *J* = 15.8 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 5.09 (br s, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.52 (q, *J* = 6.5 Hz, 2H), 3.13 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 157.2, 143.5, 137.4, 127.6, 125.4, 124.4, 122.0, 118.2, 118.1, 113.3, 113.0, 52.0, 51.7, 41.3, 28.2; IR (ATR) 3329, 3212, 2948, 1689, 1526, 1251, 1161, 1042, 977, 746, 727 cm^{-1}; HRMS (ESI) calcd for

$C_{16}H_{18}N_2NaO_4$ ($M+Na^+$) 325.1164, found 325.1159.

{2-[4-(3-Hydroxy-3-methyl-but-1-enyl)-1H-indol-3-yl]-ethyl}-carbamic acid methyl ester (61)

Methylmagnesium bromide (3.0 M in diethyl ether, 0.38 mL, 1.13 mmol) was added to a solution of **75** (34 mg, 0.11 mmol) in THF (4 mL) at 0 ^oC under N_2. The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3x10 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 2:1) gave **61** (13.2 mg, 0.044 mmol, 39 %) as a yellow solid.

Spectral data for **61**: mp 100-100.5 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1H), 7.41 (d, *J* = 15.7 Hz, 1H), 7.25 (d, *J* = 6.7 Hz, 1H), 7.11-7.21 (m, 2H), 7.00 (s, 1H), 6.32 (d, *J* = 15.7 Hz, 1H), 5.04 (br s, 1H), 3.68 (s, 3H), 3.36-3.47 (m, 2H), 3.05-3.13 (m, 2H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 140.4, 137.1, 131.7, 124.6, 124.2, 123.2, 122.3, 117.5, 113.4, 110.2, 70.9, 52.2, 43.0, 30.0, 28.8; IR (ATR) 3392, 2967, 1701, 1525, 1264, 1148, 969, 748 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}N_2NaO_3$ ($M+Na^+$) 325.1528, found 325.1526.

Acetic acid 1,4-dimethyl-2,5-dioxo-pyrrolidin-3-yl ester (86)

A mixture of 2-hydroxy-3-methyl-succinic acid **(83)** (200 mg, 1.35 mmol) and AcCl (0.79 mL) was heated at 45 ℃ for 1 h, then another 0.51 mL of AcCl was added and heated for another 4 h. The solvent was removed on a rotary evaporator at water aspirator pressure, and the residue was dissolved in CH_2Cl_2 (3 mL) and cooled to -78 ℃. To this was added a solution of methylamine (2.0 M in THF, 0.83 mL) at -78 ℃. The resulting mixture was

allowed to warm to room temperature and stirred overnight. The solvents were removed on a rotary evaporator at water aspirator pressure and AcCl (1.7 mL) was added. The resulting mixture stirred at 50 ℃ for 11 h. The AcCl was removed and purification by chromatography (hexanes/EtOAc, 4:1) gave **86** (165 mg, 0.89 mmol, 66 %, ***dr*** = 15:1) as a colorless oil.

Spectral data for major isomer of **86**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (d, *J* = 8.4 Hz, 1H), 3.11 (pent, *J* = 7.8 Hz, 1H), 2.99 (s, 3H), 2.15 (s, 3H), 1.14 (d, *J* = 7.6 Hz, 3H).

Partial spectral data for minor isomer of **86**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (d, *J* = 5.2 Hz, 1H), 2.75-2.82 (m, 1H), 1.39 (d, *J* = 7.5 Hz, 3H).

Acetic acid 3-acetoxy-1,4-dimethyl-5-oxo-pyrrolidin-2-yl ester (82)

To a solution of **86** (400 mg, 2.16 mmol) in MeOH (5 mL) was added sodium borohydride (122.72 mg, 3.24 mmol) in one portion at -40 ℃. After stirring for 10 min at -40 ℃, saturated NH_4Cl (10 mL) was added and the solution was extracted with EtOAc (4x10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure giving crude product as a white solid. The product was dissolved in CH_2Cl_2 (3.75 mL) and added DMAP (14.67 mg, 0.12 mmol). The mixture was cooled to 0 ℃ and added acetic anhydride (0.34 mL, 3.59 mmol) followed by triethylamine (0.5 mL, 3.58 mmol). Then the mixture was warmed to room temperature and stirred for 2.5 h. Brine (15 mL) was added, and the solution was extracted by EtOAc (3x15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 2:1) gave **82** (146 mg, 0.64 mmol, 29 %) as a colorless oil.

Spectral data for **82**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (d, *J* = 5.4 Hz, 1H), 5.28 (dd, *J* =

8.2, 5.3 Hz, 1H), 2.82 (s, 3H), 2.70 (pent, *J* = 7.8 Hz, 1H), 2.06 (s, 3H), 2.04 (s, 3H), 1.17 (d, *J* = 7.6 Hz, 3H).

Acetic acid 2-(2-bromo-allyl)-1,4-dimethyl-5-oxo-pyrrolidin-3-yl ester (81)

A solution of **82** (121 mg, 0.53 mmol) and 2-bromo-2-propen-1-yl trimethylsilane **(13)** (365 μL, 2.12 mmol) in CH_2Cl_2 (2.74 mL) was cooled to -78 ℃ and stirred for 15 min. A solution of $TiCl_4$ (116.4 μL, 1.06 mmol) in CH_2Cl_2 (1.37 mL) was added slowly. The cold bath was removed after 30 min, and the mixture was stirred at ambient temperature for an additional 1 h. $Na_2CO_3 \cdot 10H_2O$ (1.76 g) was added slowly. After stirring for 30 min, the mixture was dried ($MgSO_4$) and filtered, and the solvent was removed. Purification by chromatography (hexanes/EtOAc, 2:1) gave **81** (144 mg, 0.50 mmol, 94 %) as a colorless oil.

Spectral data for **81**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71-5.74 (m, 1H), 5.57 (d, *J* = 2.0 Hz, 1H), 5.20 (d, *J* = 6.2 Hz, 1H), 3.65-3.71 (m, 1H), 2.89 (d, *J* = 0.8 Hz, 3H), 2.67-2.78 (m, 2H), 2.59 (ddd, *J* = 14.6, 7.3, 0.9 Hz, 1H), 2.07 (s, 3H), 1.10 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 170.2, 128.2, 120.7, 73.1, 63.5, 42.3, 38.5, 28.7, 20.7, 8.7.

Acetic acid 1,4-dimethyl-5-oxo-2-(2-trimethylstannanyl-allyl)-pyrrolidin-3-yl ester (87)

A solution of **81** (30 mg, 0.10 mmol), $Pd(dba)_2$ (4.44 mg, 0.0078 mmol), hexamethylditin (67.78 mg, 0.21 mmol), triphenylphosphine (5.43 mg, 0.021 mmol) and DIPEA (3.6 μL, 0.021 mmol) in benzene (0.6 mL) was stirred at 80 ℃ for 4 h. The mixture was cooled to ambient temperature and purified by chromatography (hexanes/EtOAc, 2:1) to afford **87** (26 mg, 0.07 mmol, 67 %) as a yellow oil.

Spectral data for **87**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, *J* = 1.2 Hz, 1H), 5.35 (d, *J* = 1.9 Hz, 1H), 5.20 (d, *J* = 6.1 Hz, 1H), 3.38 (dd, *J* = 9.4, 4.7 Hz, 1H), 2.87 (s, 3H), 2.65-2.76 (m,

2H), 2.26 (dd, *J* = 14.0, 9.6 Hz, 1H), 2.04 (s, 3H), 1.08 (d, *J* = 7.4 Hz, 3H), 0.17 (s, 9H).

Acetic acid 2-{2-[2-(4-methoxy-benzyloxy)-6-nitro-phenyl]-allyl}-1,4-dimethyl-5-oxo-pyrrolidin-3-yl ester (80)

A solution of **81** (16 mg, 0.055 mmol), **64** (28 mg, 0.066 mmol), $Pd(dba)_2$ (1.6 mg, 0.0028 mmol), triphenylphosphine (2.89 mg, 0.011 mmol), and copper (I) iodide (7.88 mg, 0.041 mmol) in DMF (1 mL) was stirred at room temperature for 22 h. The reaction was diluted with H_2O (5 mL) and extracted with EtOAc (3x5 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 10:1, then hexanes/EtOAc, 2:1) gave **80** (15.6 mg, 0.033 mmol, 60 %) as a yellow oil.

Spectral data for **80**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 3.6 Hz, 1H), 7.37 (d, *J* = 5.7 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.16 (dd, *J* = 5.7, 3.7 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.36 (d, *J* = 5.8 Hz, 1H), 5.23 (s, 1H), 5.05 (d, *J* = 11.2 Hz, 1H), 5.03 (s, 1H), 5.00 (d, *J* = 11.1 Hz, 1H), 3.82 (s, 3H), 3.67 (dd, *J* = 11.1, 3.1 Hz, 1H), 2.70-2.86 (m, 4H), 2.38 (br s, 2H), 2.03 (s, 3H), 0.96 (d, *J* = 5.3 Hz, 3H).

5-{2-[2-(4-Methoxy-benzyloxy)-6-nitro-phenyl]-allylidene}-1,3-dimethyl-1,5-dihydro-pyrrol-2-one (89) and tricyclic compound 90

To a solution of **80** (15 mg, 0.032 mmol) in toluene (0.65 mL) was added DBU (5.27 μL, 0.035 mmol). The mixture was stirred at 110 ℃ for 12 h, then cooled to room temperature. Purification by chromatography (hexanes/EtOAc, 3:1) gave **89** (1.4 mg, 0.0034 mmol, 11 %) followed by **90** (0.4 mg, 0.0011 mmol, 3 %), then (hexanes/EtOAc, 2:1) gave **80** (3.7 mg, 0.0079 mmol, 25 %).

Spectral data for **89**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.10 (s, 1H), 6.05-6.07 (m, 1H), 5.48 (s, 1H), 5.12 (s, 1H), 5.01 (s, 2H), 3.79 (s, 3H), 3.14 (s, 3H), 1.78 (d, *J* = 1.2 Hz, 3H).

Spectral data for **90**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.5 Hz, 2H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 1.6 Hz, 1H), 6.43 (d, *J* = 8.2 Hz, 1H), 6.21 (d, *J* = 8.1 Hz, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 5.15 (s, 1H), 5.03 (s, 2H), 3.82 (s, 3H), 2.89 (s, 3H), 2.84 (d, *J* = 13.4 Hz, 1H), 2.49 (d, *J* = 13.2 Hz, 1H), 1.89 (d, *J* = 1.2 Hz, 3H).

N-Allyl-2-methyl-N-(1-phenyl-ethyl)-acrylamide (92)

To a solution of sodium hydride (60 % dispersion in mineral oil, 3.47 g, 144.58 mmol) in DMF (44 mL) was added **91** (8.22 g, 43.42 mmol) in DMF (46 mL) dropwisely at 0 ℃. After addition, the mixture was warmed to room temperature and stirred for 30 min. Then the mixture was cooled to 0 ℃ and added allyl bromide (6.16 mL, 71.18 mmol) in DMF (44 mL) slowly. Then the mixture was warmed to room temperature again and stirred for 1 h; brine (200 mL) was added, and the mixture was extracted with EtOAc (3x150 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed at reduced pressure. Purification by chromatography (hexanes/EtOAc, 10:1) gave **92** (5.65 g, 24.60 mmol, 57 %) as a pale yellow oil.

Spectral data for **92**: ^{1}H NMR (400 MHz, $CDCl_3$, 65 ℃) δ 7.21-7.33 (m, 5H), 5.62-5.76 (m, 1H), 5.58 (s, 1H), 5.13 (s, 1H), 5.08 (s, 1H), 4.99 (s, 1H), 4.95 (s, 1H), 3.98 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.50 (dd, *J* = 16.0, 5.6 Hz, 1H), 1.99 (s, 3H), 1.58 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 141.2, 140.6, 135.2, 128.2, 127.1, 126.9, 115.8, 114.2, 54.1, 45.6, 20.3, 17.6; IR (ATR) 2978, 1619, 1451, 1409, 1201, 910, 697 cm^{-1}; $[\alpha]^{25}_{D}$ = -106.6 ±

0.1 (*c* 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{20}NO$ ($M+H^+$) 230.1545, found 230.1538.

3-Methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one (93)

To a solution of **92** (288 mg, 1.26 mmol) in anhydrous CH_2Cl_2 (43 mL) was added Grubbs catalyst, 1st generation (103.3 mg, 0.13 mmol). The mixture was stirred at 45 ℃ for 13 h and then allowed to cool to ambient temperature. The solvent was removed at reduced pressure and the resulting residue was purified by chromatography (hexanes/EtOAc = 5:1) to give **93** (220 mg, 1.09 mmol, 87 %) as a brown solid.

Spectral data for **93**: mp 67.5-68.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.34 (m, 4H), 7.18-7.24 (m, 1H), 6.60 (d, *J* = 1.3 Hz, 1H), 5.54 (q, *J* = 7.1 Hz, 1H), 3.76 (td, *J* = 19.7, 1.7 Hz, 1H), 3.45 (td, *J* = 19.6, 1.7 Hz, 1H), 1.90 (d, *J* = 1.7 Hz, 3H), 1.57 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 140.7, 134.9, 134.9, 134.8, 128.0, 126.8, 126.4, 48.8, 46.0, 17.2, 10.8; IR (ATR) 3425, 2986, 1663, 1452, 1402, 1224, 819, 790, 762, 700, 678 cm^1; HRMS (ESI) calcd for $C_{13}H_{16}NO$ ($M+H^+$) 202.1232, found 202.1225.

5-Hydroxy-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one (94)

To a solution of LDA (1.5 M in tetrahydrofuran/ethylbenzene/heptane, 0.19 mL) in THF (0.85 mL) was added a solution of **93** (57 mg, 0.28 mmol) in THF (1.02 mL) at 0 ℃. The mixture was stirred at 0 ℃ for 3 h, then charged in O_2 and stirred for additional 30 min. The reaction was quenched by NH_4Cl (5 mL), then warmed to room temperature and extracted by EtOAc (3x5 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 4:1) to give **94** (30 mg, 0.14 mmol, 49 %) as a colorless oil.

Spectral data for the major isomer of **94**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.50 (m, 5H), 6.46 (d, *J* = 1.6 Hz, 1H), 5.43 (d, *J* = 9.7 Hz, 1H), 5.17 (q, *J* = 7.2 Hz, 1H), 2.70 (d, *J* = 10.0 Hz, 1H), 1.84 (s, 3H), 1.74 (d, *J* = 7.3 Hz, 3H).

Partial spectral data for the minor isomer of **94**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36-6.39 (m, 1H), 5.33 (q, *J* = 7.4 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 2.96 (d, *J* = 10.6 Hz, 1H), 1.84 (s, 3H), 1.72 (d, *J* = 7.3 Hz, 3H).

Spectral data for mixture of both isomers of **94**: IR (ATR) 3339, 2923, 1676, 1653, 1449, 1397, 1359, 1226, 1053, 699 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}NNaO_2$ ($M+Na^+$) 240.1000, found 240.0994.

5-(2-Bromo-allyl)-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one (95)

A solution of **94** (105 mg, 0.48 mmol) and 2-bromo-2-propen-1-yl trimethylsilane **(13)** (334 μL, 1.94 mmol) in CH_2Cl_2 (7.8 mL) was cooled to -78 ℃ and stirred for 15 min. $TiCl_4$ (106 μL, 0.97 mmol) was added slowly under a N_2 atmosphere. The cold bath was removed after 30 min, and the mixture was stirred at ambient temperature for an additional 1 h. $Na_2CO_3 \cdot 10H_2O$ (1.67 g) was added slowly. After stirring for 30 min, the mixture was dried ($MgSO_4$) and filtered. The solvents were removed and the crude product was purified by chromatography on silica gel (hexanes/EtOAc, 10:1) to give **95** (119 mg, 0.37 mmol, 77 %, ***dr*** = 3:1) as a colorless oil.

Spectral data for the major isomer of **95**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.47 (m, 5H), 6.70 (s, 1H), 5.40-5.52 (m, 3H), 4.32-4.44 (m, 1H), 2.46 (dd, *J* = 14.0, 3.9 Hz, 1H), 1.92 (s, 3H), 1.88 (dd, *J* = 13.9, 10.6 Hz, 1H), 1.73 (d, *J* = 7.3 Hz, 3H).

Partial spectral data for the minor isomer of **95**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 1H), 5.37 (q, *J* = 7.4 Hz, 1H), 3.95-4.03 (m, 1H), 3.00 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.25 (dd, *J* = 13.5, 10.7 Hz, 1H), 1.90 (d, *J* = 1.2 Hz, 3H). 1.69 (d, *J* = 7.2 Hz, 3H).

Spectral data for the mixture of both isomers of **95**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 171.8, 141.6, 140.1, 139.3, 139.3, 139.2, 139.2, 134.8, 134.7, 128.7, 128.4, 128.3, 128.2, 127.3, 127.1, 127.1, 126.8, 119.6, 58.4, 57.3, 51.4, 49.3, 44.4, 44.1, 18.5, 17.1, 11.0, 11.0; IR (ATR) 2975, 1677, 1397, 1229, 894, 836, 754, 699 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}BrNO$ ($M+H^+$) 320.0650, found 320.0642.

5-[2-(2-Methoxymethoxy-6-nitro-phenyl)-allyl]-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one (96)

A solution of **95** (106 mg, 0.33 mmol), **67** (137.43 mg, 0.40 mmol), $Pd(dba)_2$ (9.52 mg, 0.017 mmol), triphenylphosphine (17.35 mg, 0.066 mmol), and copper (I) iodide (47.3 mg, 0.25 mmol) in DMF (6 mL) was stirred at room temperature for 24 h. The reaction was diluted with H_2O (15 mL) and extracted with EtOAc (3x15 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 2:1) gave **96** (105 mg, 0.25 mmol, 75 %, ***dr*** = 3:1) as a yellow oil.

Spectral data for the major isomer of **96**: ^{1}H NMR (400 MHz, $CDCl_3$, 65 ℃) δ 7.13-7.36 (m, 8H), 6.83 (s, 1H), 5.28 (q, *J* = 7.2 Hz, 1H), 5.17 (s, 1H), 4.98-5.09 (m, 2H), 4.96 (s, 1H), 4.21 (d, *J* = 11.5 Hz, 1H), 3.33 (s, 3H), 2.79 (d, *J* = 14.7 Hz, 1H), 1.91 (dd, *J* = 14.8, 11.7 Hz, 1H), 1.88 (s, 3H), 1.64 (d, *J* = 7.3 Hz, 3H).

Spectral data for the minor isomer of **96**: ^{1}H NMR (400 MHz, $CDCl_3$, 65 °C) δ 7.13-7.36 (m, 8H), 6.78 (s, 1H), 5.33 (q, *J* = 7.3 Hz, 1H), 5.11 (s, 1H), 4.98-5.09 (m, 2H), 4.92 (s,

1H), 3.81 (d, *J* = 10.5 Hz, 1H), 3.36 (s, 3H), 3.19 (d, *J* = 14.8 Hz, 1H), 2.19 (dd, *J* = 14.4, 11.6 Hz, 1H), 1.88 (s, 3H), 1.67 (d, *J* = 7.3 Hz, 3H).

Spectral data for the mixture of both isomers of **96**: HRMS (ESI) calcd for $C_{24}H_{27}N_2O_5$ ($M+H^+$) 423.1920, found 423.1918.

5-[2-(2-Hydroxy-6-nitro-phenyl)-allyl]-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one (97)

To a stirred solution of the **96** (29 mg, 0.069 mmol) in CH_2Cl_2 (0.75 mL) was added activated (while hot) $NaHSO_4{\cdot}SiO_2$ (27.5 mg, 0.15 mmol) (the catalyst was kept in an oven at 120 ℃ for 48 h before using it) at room temperature. After completion of the reaction (monitored by TLC, overnight), the catalyst was filtered off and washed with CH_2Cl_2 (2x2 mL). The filtrate and washings were combined, and the solvents were removed under vacuum. Purification by chromatography (hexanes/EtOAc, 1:1) gave **97** (24 mg, 0.063 mmol, 92 %, ***dr*** = 3:1) as a colorless oil.

Spectral data for the major isomer of **97**: ^{1}H NMR (600 MHz, $CDCl_3$, 65 °C) δ 7.11-7.43 (m, 8H), 6.70 (s, 1H), 5.25 (q, *J* = 7.2 Hz, 1H), 5.16 (s, 1H), 5.05 (s, 1H), 4.18 (d, *J* = 10.0 Hz, 1H), 2.77 (d, *J* = 14.8 Hz, 1H), 2.10 (dd, *J* = 14.0, 11.2 Hz, 1H), 1.80 (s, 3H), 1.65 (d, *J* = 7.3 Hz, 3H).

Spectral data for the minor isomer of **97**: ^{1}H NMR (600 MHz, CDCl3, 65 °C) δ 7.11-7.43 (m, 8H), 6.73 (s, 1H), 5.31 (q, *J* = 7.1 Hz, 1H), 5.23 (s, 1H), 5.06 (s, 1H), 3.81 (d, *J* = 10.7 Hz, 1H), 3.16 (d, *J* = 14.3 Hz, 1H), 2.29 (dd, *J* = 12.8, 11.6 Hz, 1H), 1.82 (s, 3H), 1.66 (d, *J* = 7.5 Hz, 3H).

Trifluoro-methanesulfonic acid 2-{1-[4-methyl-5-oxo-1-(1-phenyl-ethyl)-2,5-dihydro-1H-pyrrol-2-ylmethyl]-vinyl}-3-nitro-phenyl ester (98)

N-Phenyl-bis(trifluoromethanesulfonimide) (23 mg, 0.064 mmol) was added to a solution of **97** (24 mg, 0.063 mmol) and K_2CO_3 (13 mg, 0.094 mmol) in DMF (0.35 mL). The mixture was stirred at room temperature for 30 min. The reaction was diluted with H_2O (2 mL) and extracted with EtOAc (3x2 mL), dried ($MgSO_4$) and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 2:1) gave **98** (31 mg, 0.061 mmol, 96 %, ***dr*** = 3:1) as a yellow oil.

Spectral data for major isomer of **98**: ^{1}H NMR (600 MHz, $CDCl_3$, 65 ^{o}C) δ 7.84 (d, *J* = 6.8 Hz, 1H), 7.52 (t, *J* = 8.3 Hz, 1H), 7.48-7.51 (m, 1H), 7.34 (d, *J* = 7.4 Hz, 2H), 7.24 (d, *J* = 7.7 Hz, 2H), 7.15-7.18 (m, 1H), 6.84 (s, 1H), 5.41 (s, 1H), 5.35 (q, *J* = 7.3 Hz, 1H), 5.18 (s, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 2.63 (d, *J* = 13.0 Hz, 1H), 1.91 (t, *J* = 1.7 Hz, 3H), 1.84 (dd, *J* = 15.9, 11.3 Hz, 1H), 1.66 (d, *J* = 7.3 Hz, 3H).

Spectral data for minor isomer of **98**: ^{1}H NMR (600 MHz, $CDCl_3$, 65 ^{o}C) δ 7.46-7.50 (m, 1H), 7.30-7.32 (m, 1H), 7.21-7.26 (m, 3H), 7.15-7.20 (m, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 6.80 (t, *J* = 1.4 Hz, 1H), 5.37 (q, *J* = 7.3 Hz, 1H), 5.35 (s, 1H), 5.16 (s, 1H), 3.79 (d, *J* = 11.2 Hz, 1H), 3.10 (d, *J* = 10.8 Hz, 1H), 2.18 (t, *J* = 12.9 Hz, 1H), 1.90 (t, *J* = 1.7 Hz, 3H), 1.67 (d, *J* = 7.3 Hz, 3H).

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30. Mp 180−182 °C; lit. mp (ref 1) 182−184 °C.

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45. Overall yield starting from **1**.
46. A small amount of a second unidentified product was observed in the NMR spectra, but the products could not be separated by chromatography.
47. The diastereomeric ratio varied from 2:1 to 1:1 between different runs.
48. We were unable to determine *dr* due to broad unresolved NMR resonances.
49. Integration of the two resolved methyl doublets at d 1.32 and 1.27 in the ^{1}H NMR spectrum at 65 °C suggest a *dr* of 15:1.
50. Most of the ^{1}H NMR signals were unresolved even at 65 °C.

Appendix

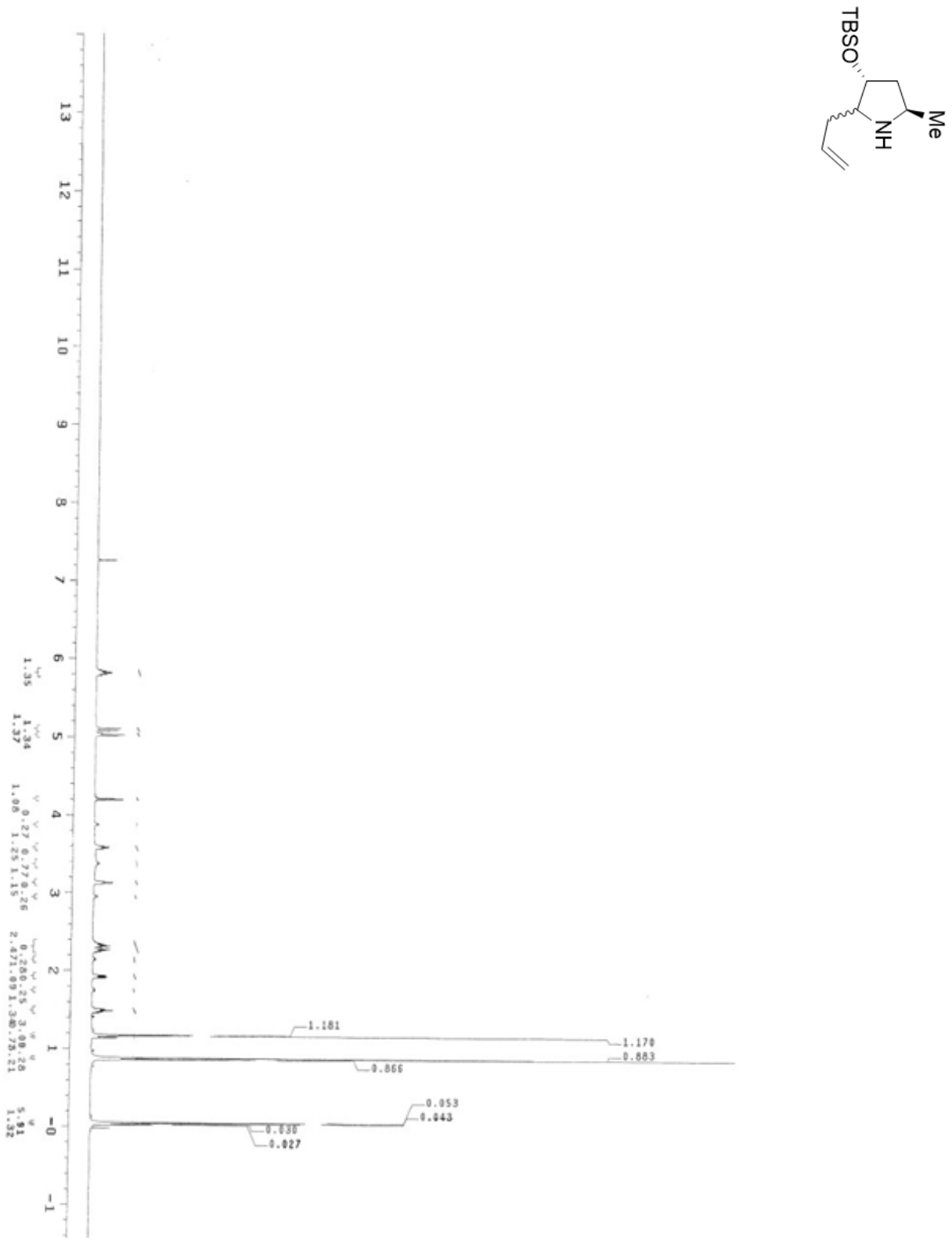

Figure 8: ^{1}H NMR of 3(R)-[(*t*-butyldimethylsilyl)oxy]-5(R)-methyl-2-(2-propen-1-yl)pyrrolidine **(5)**

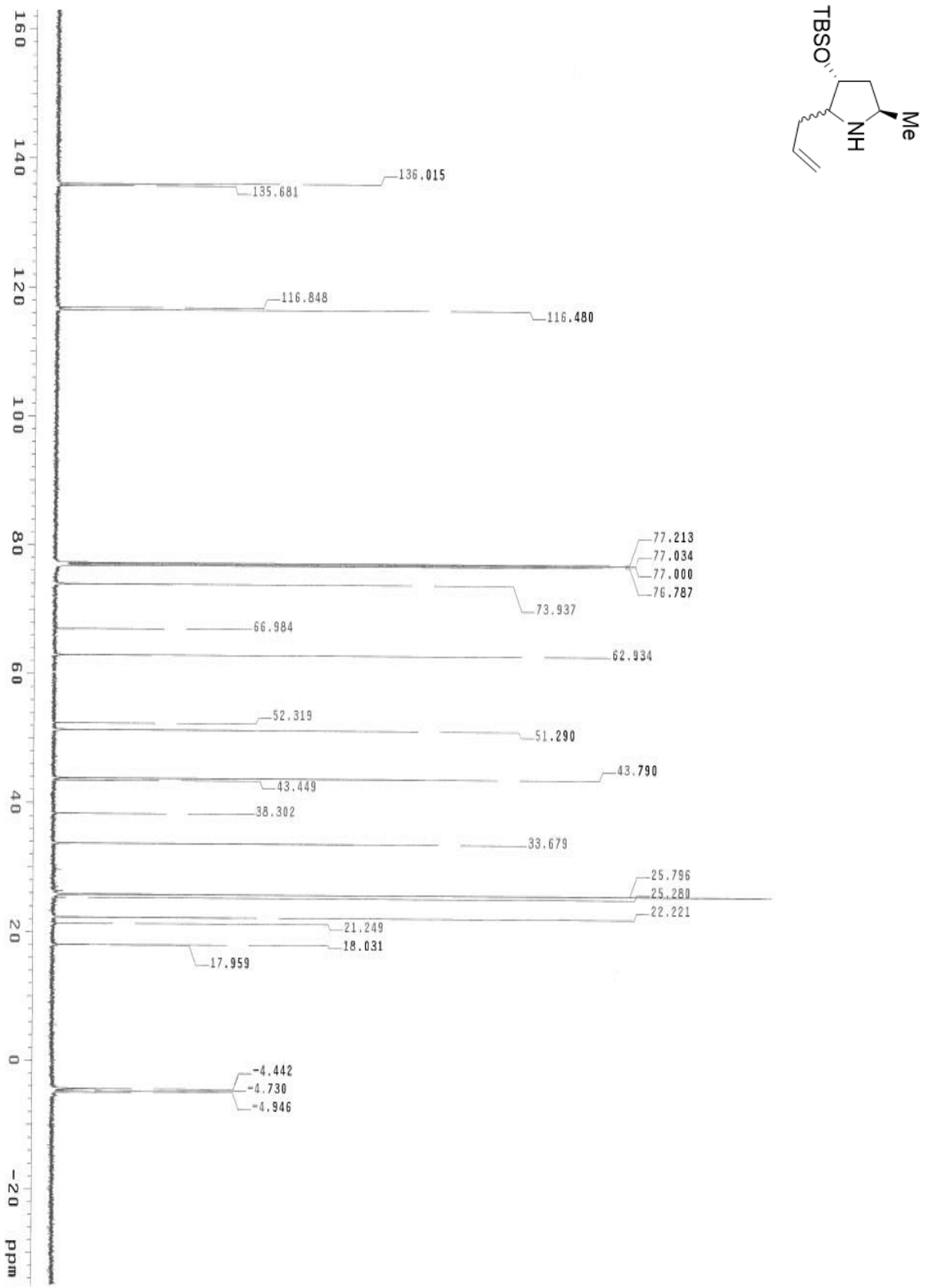

Figure 9: ^{13}C NMR of 3(R)-[(*t*-butyldimethylsilyl)oxy]-5(R)-methyl-2-(2-propen-1-yl)pyrrolidine **(5)**

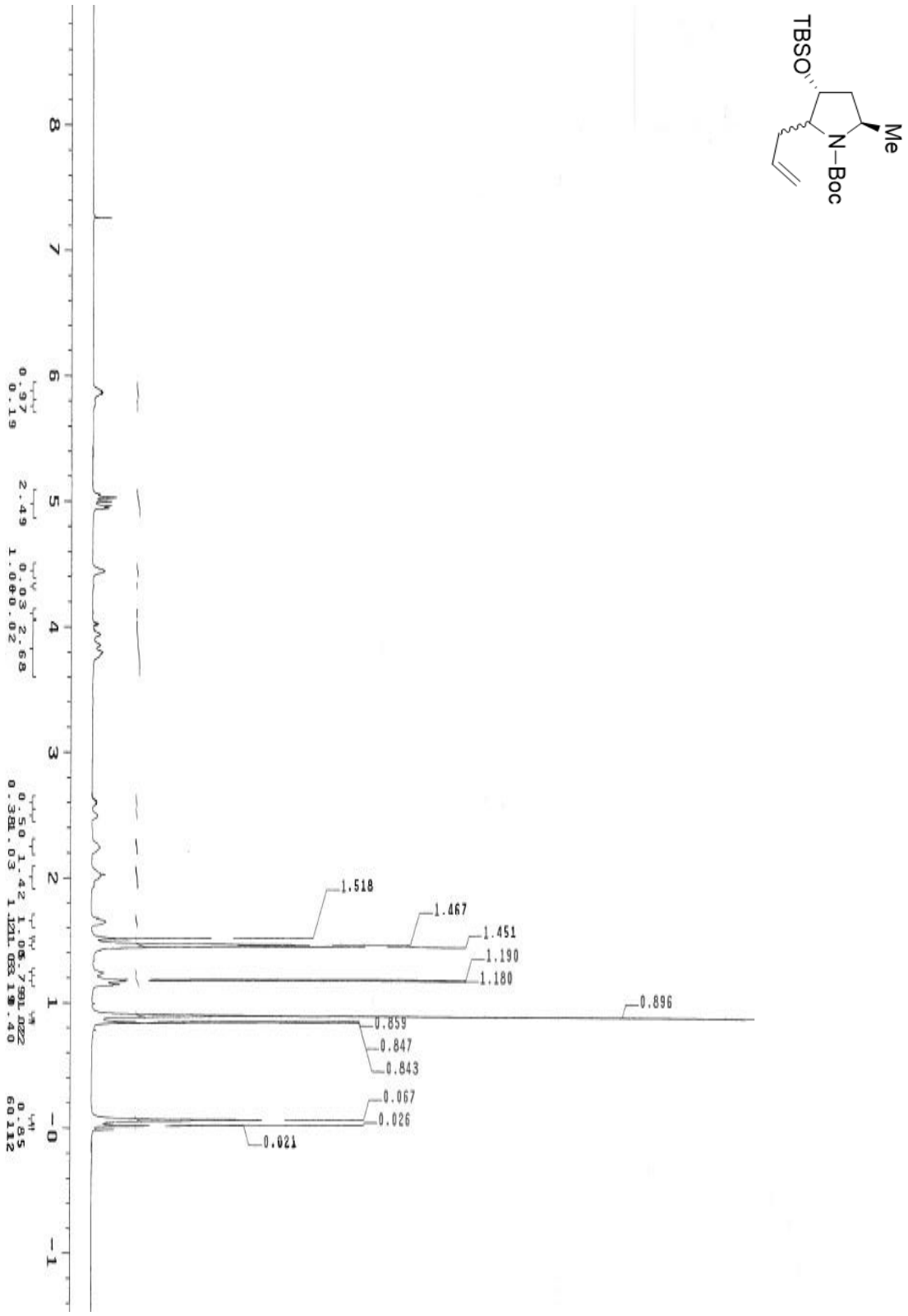

Figure 10: ^{1}H NMR of 1-(*t*-butoxycarbonyl)-3(R)-[(*t*-butyldimethylsilyl)oxy]-5(R)-methyl-2-(2-propen-1-yl)-pyrrolidine **(6)**

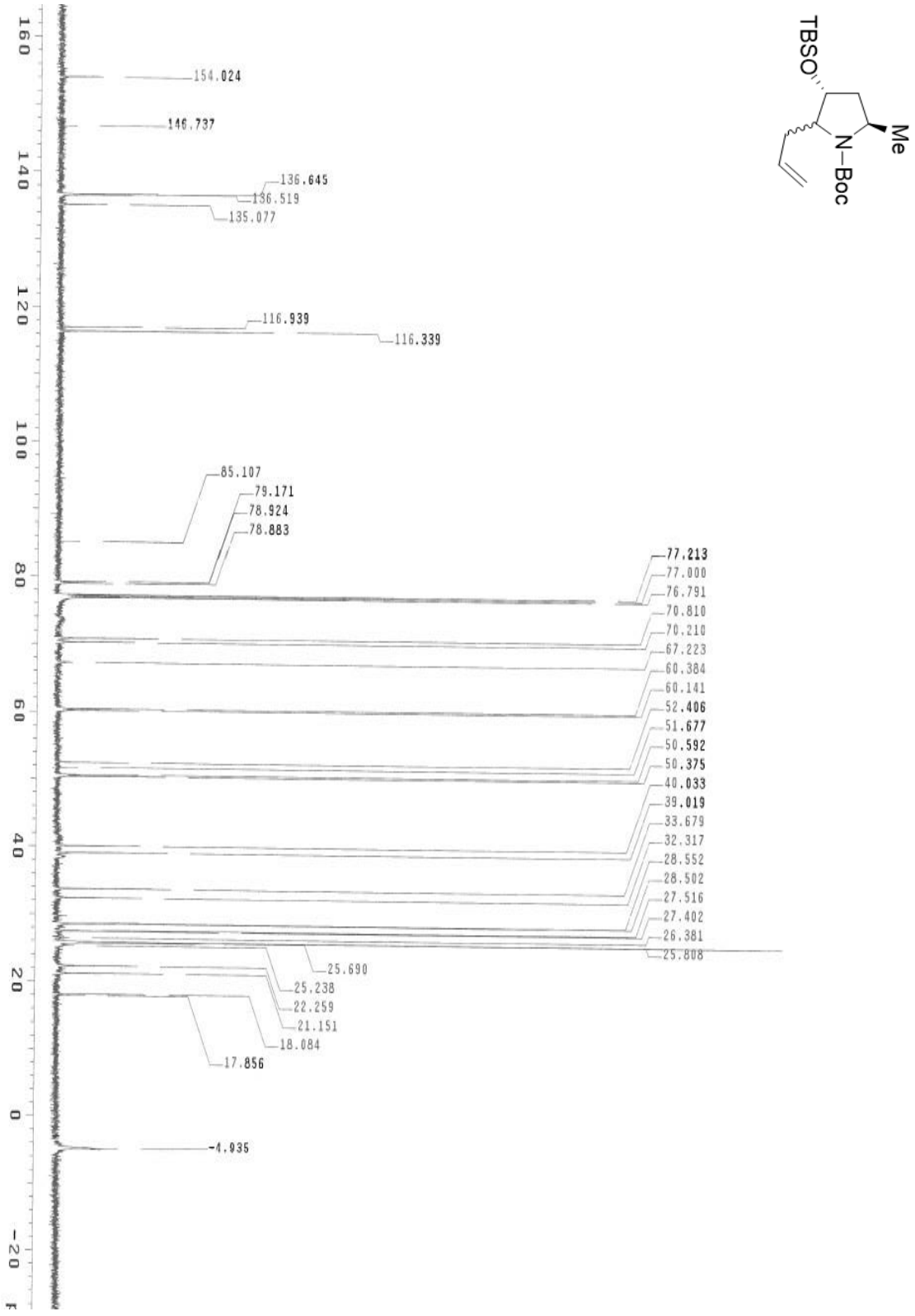

Figure 11: ^{13}C NMR of 1-(*t*-butoxycarbonyl)-3(R)-[(*t*-butyldimethylsilyl)oxy]-5(R)-methyl-2-(2-propen-1-yl)-pyrrolidine **(6)**

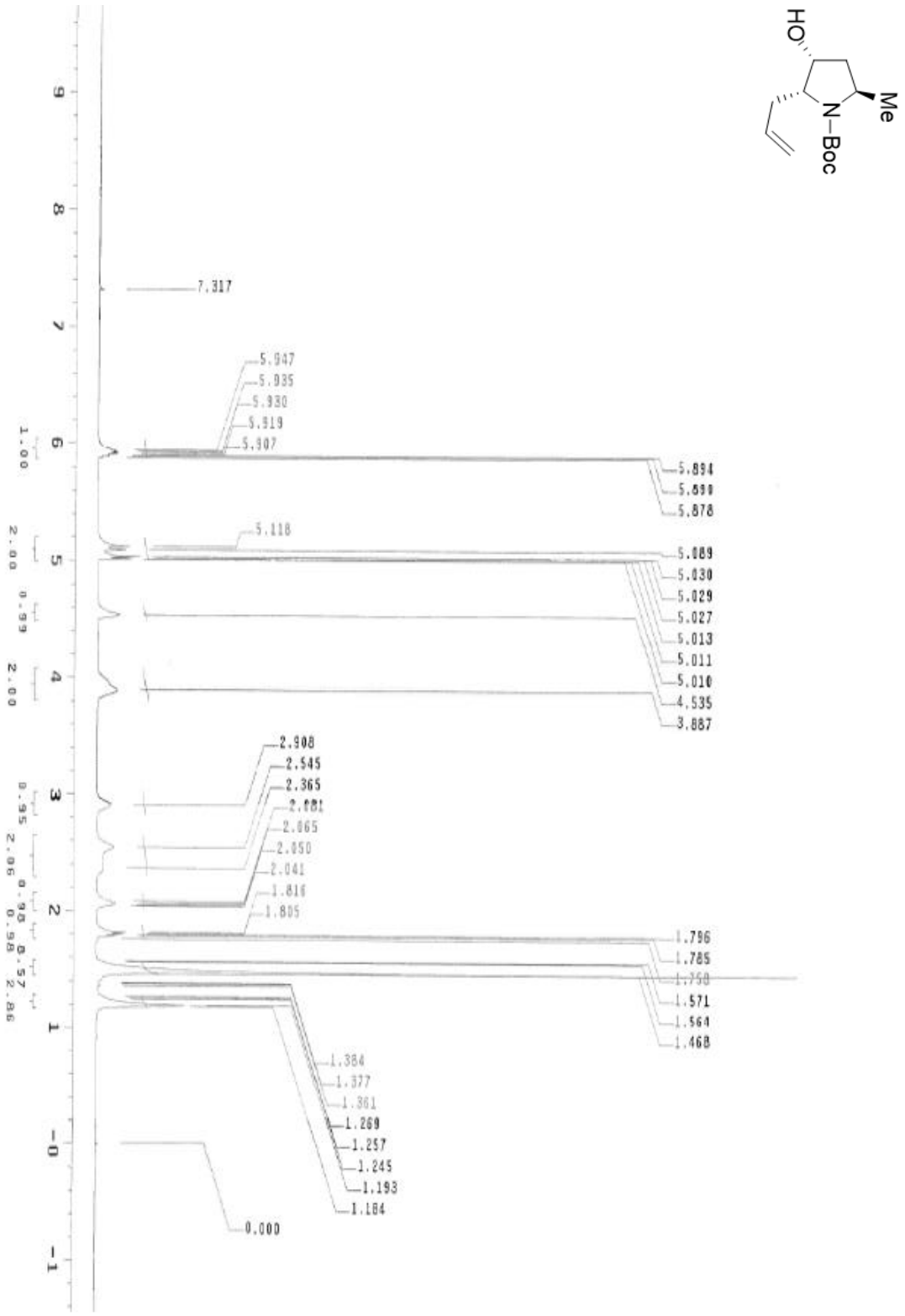

Figure 12: ^{1}H NMR of 1-(*t*-butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(R)-(2-propen-1-yl)pyrrolidine **(7)**

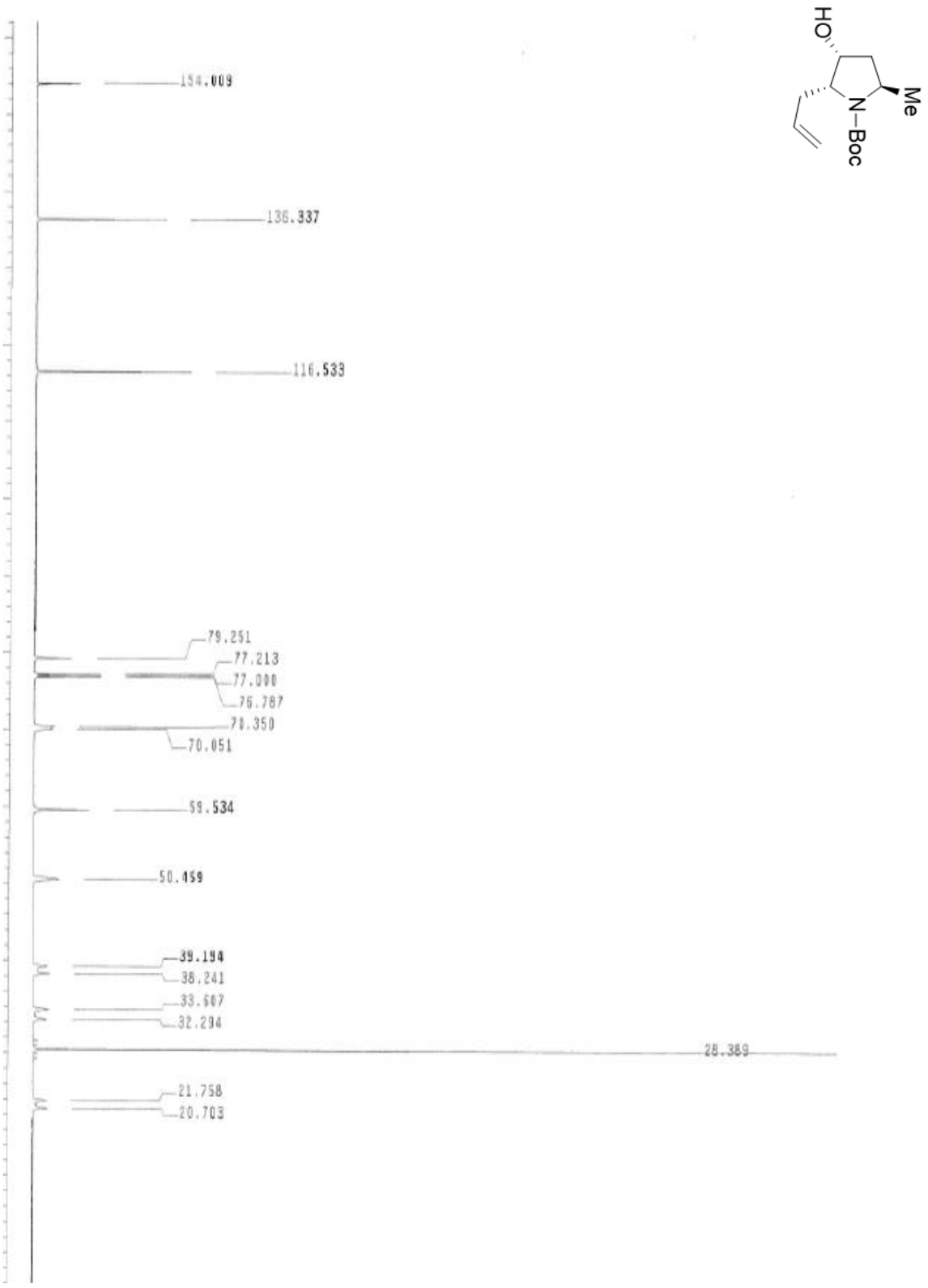

Figure 13: ^{13}C NMR of 1-(*t*-butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(R)-(2-propen-1-yl)pyrrolidine **(7)**

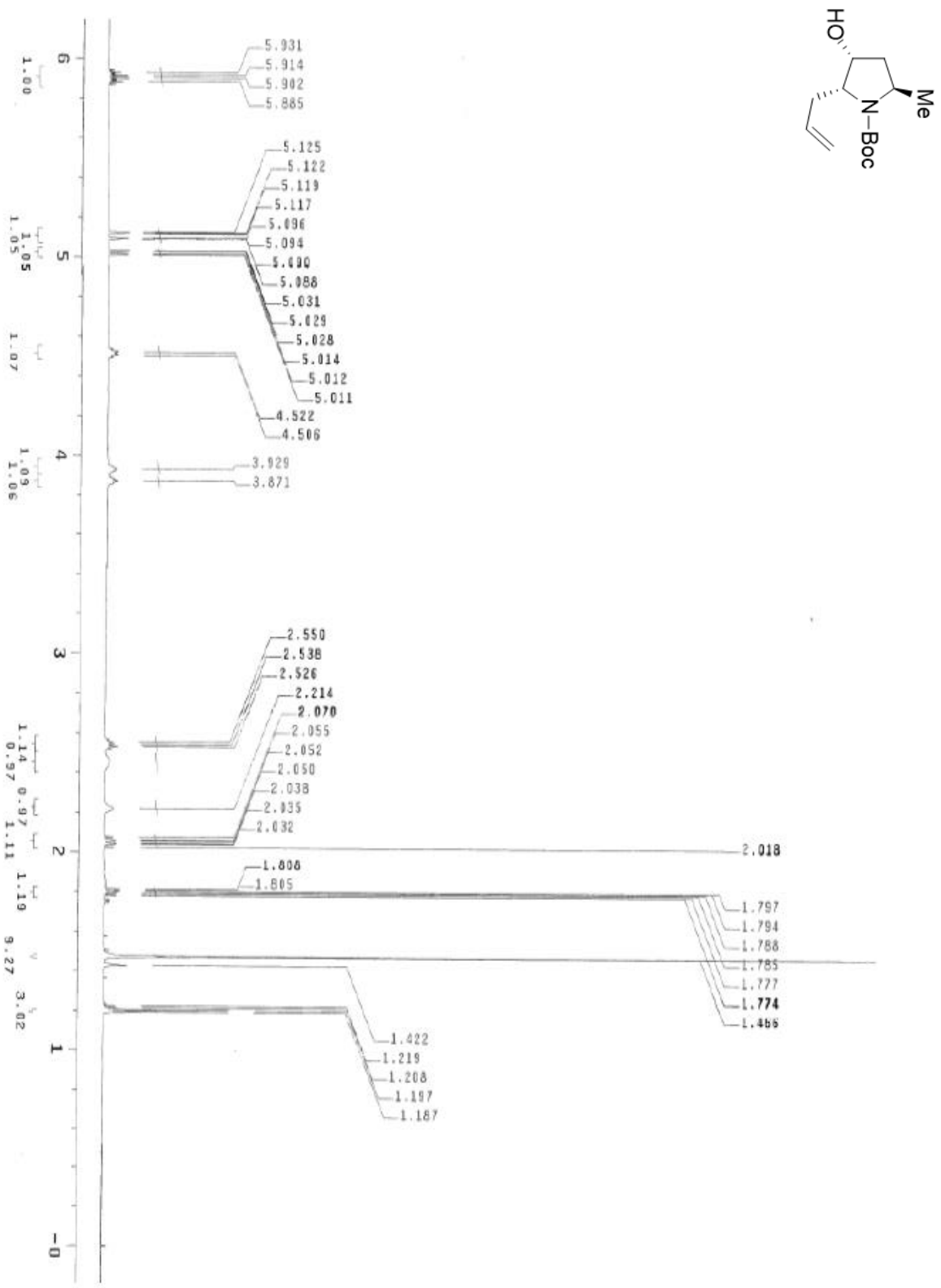

Figure 14: ^{1}H NMR (60 ℃) of 1-(*t*-butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(R)-(2-propen-1-yl)pyrrolidine **(7)**

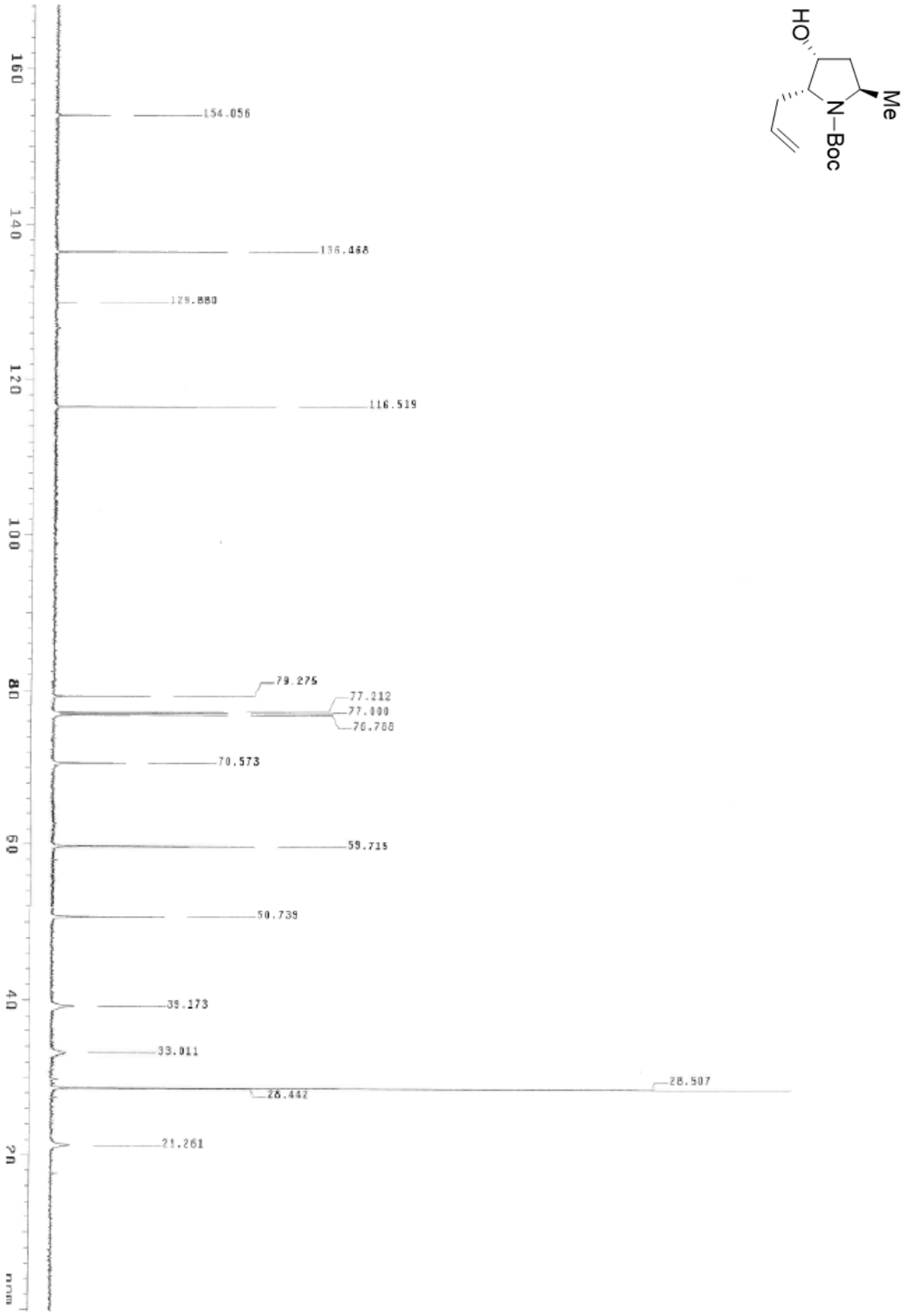

Figure 15: ^{13}C NMR (60 ℃) of 1-(*t*-butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(R)-(2-propen-1-yl)pyrrolidine **(7)**

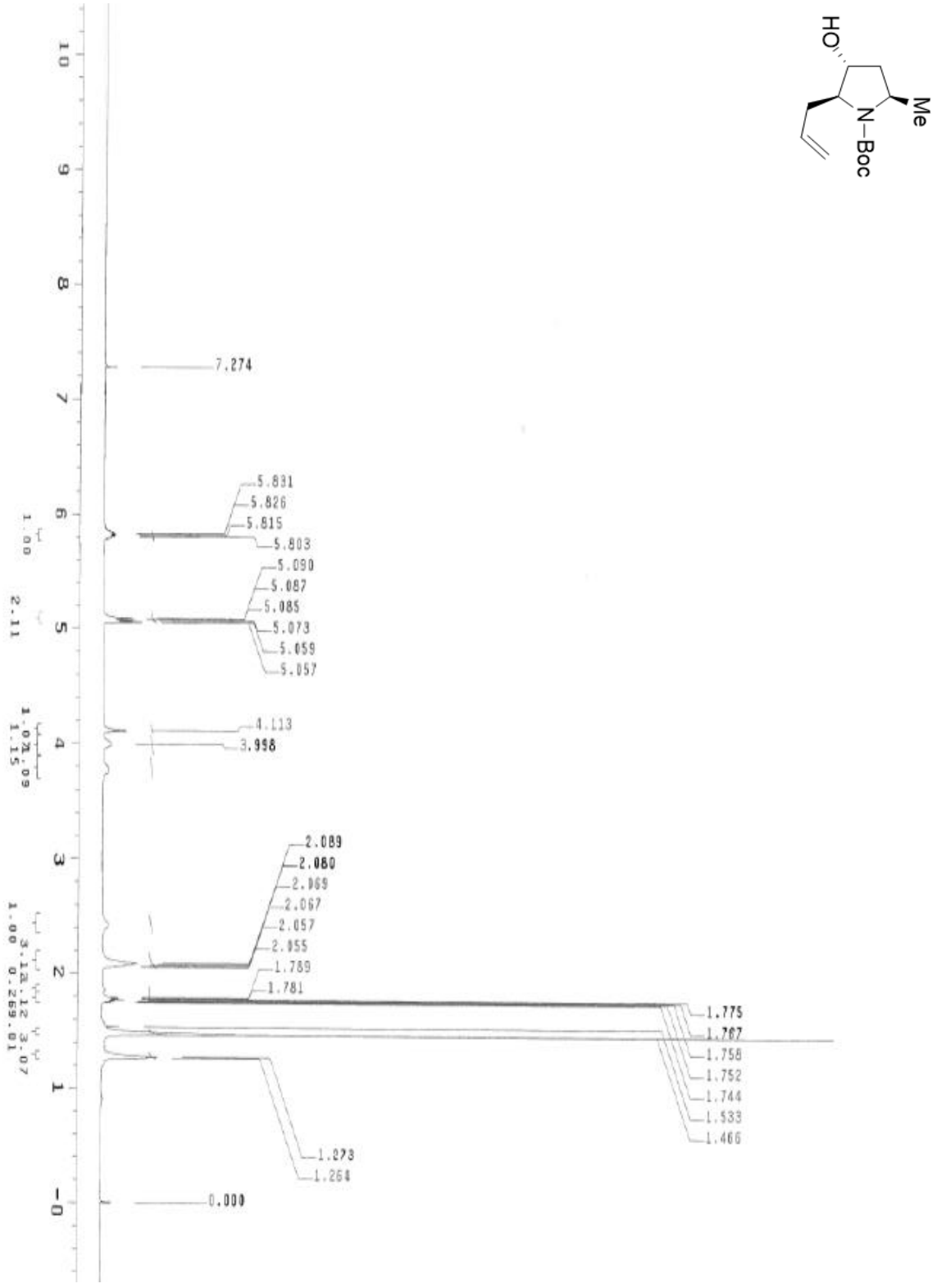

Figure 16: ^{1}H NMR of 1-(*t*-butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(S)-(2-propen-1-yl)pyrrolidine **(8)**

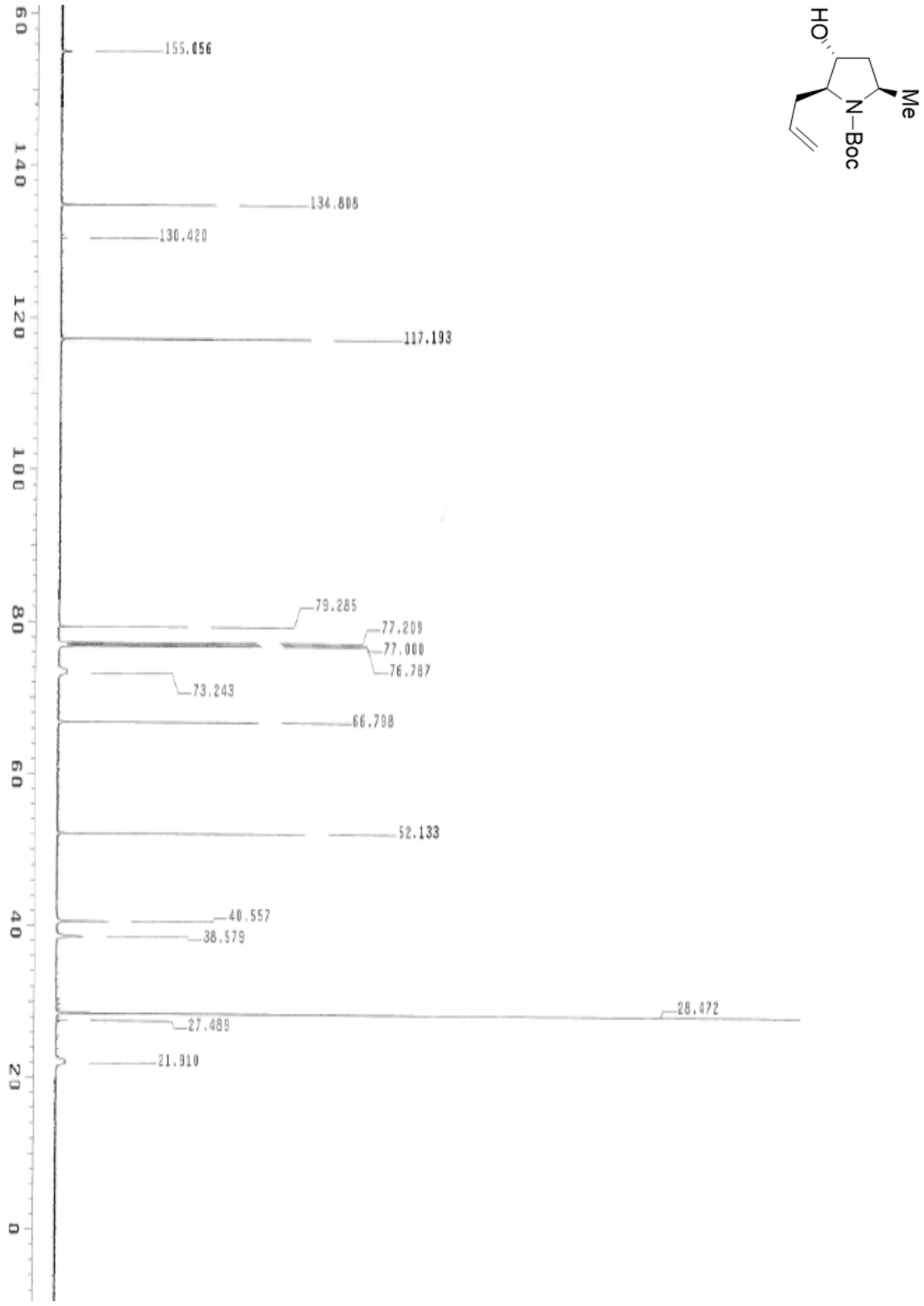

Figure 17: ^{13}C NMR of 1-(*t*-butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(S)-(2-propen-1-yl)pyrrolidine **(8)**

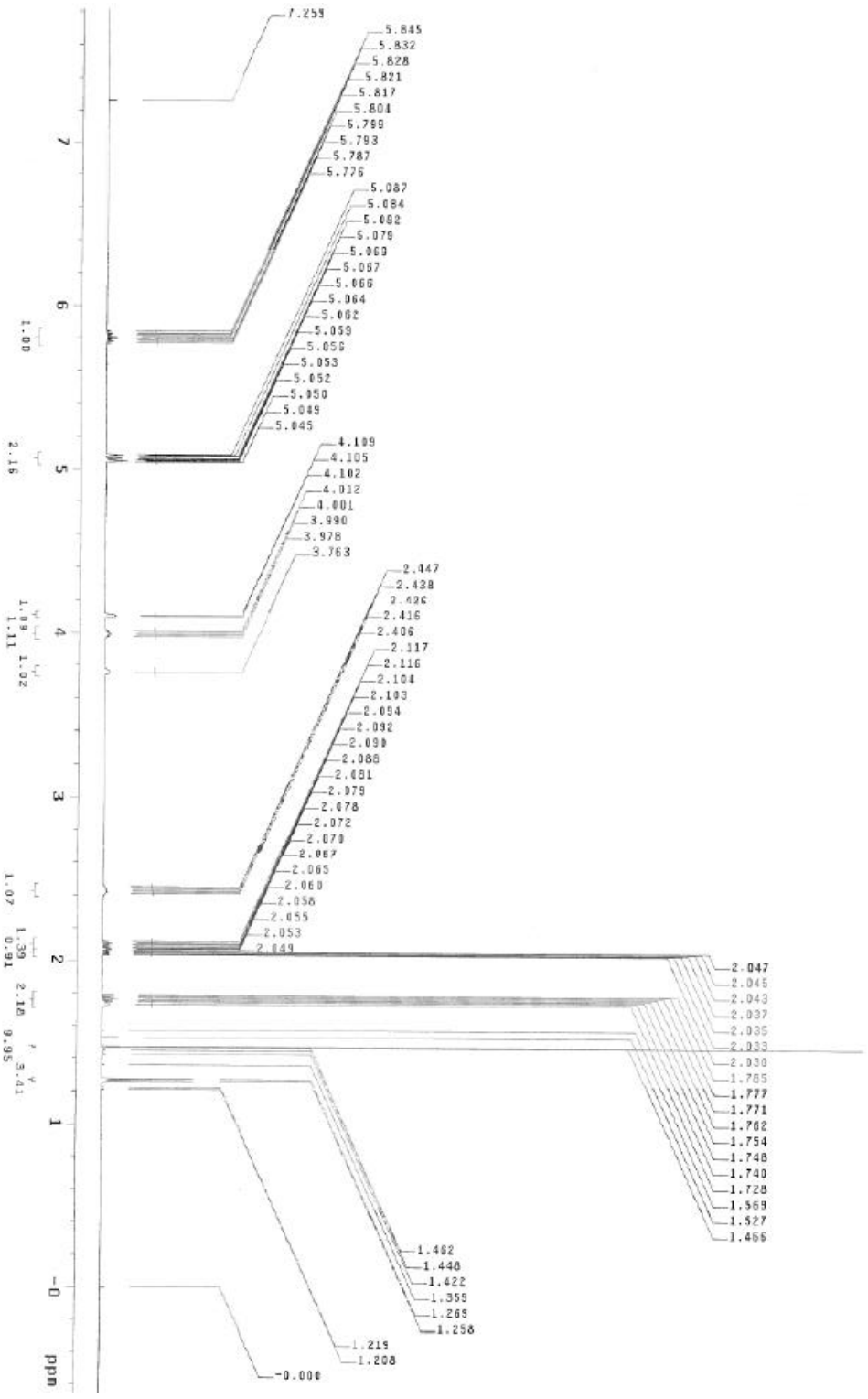

Figure 18:[1]H NMR (60 ℃) of 1-(*t*-butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(S)-(2-propen-1-yl)pyrrolidine **(8)**

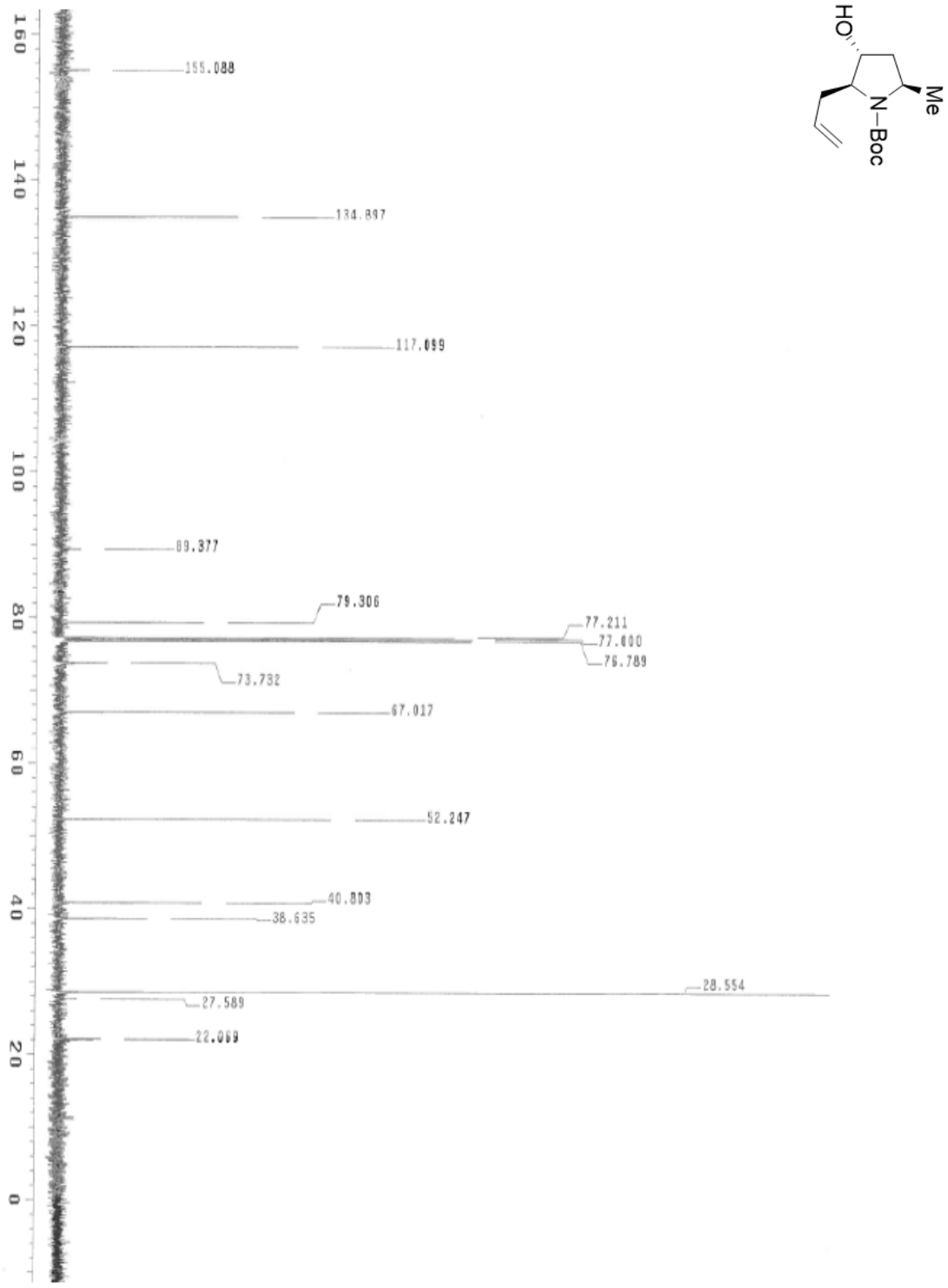

Figure 19: ^{13}C NMR (60 ℃) of 1-(*t*-butoxycarbonyl)-3(R)-hydroxy-5(R)-methyl-2(S)-(2-propen-1-yl)pyrrolidine **(8)**

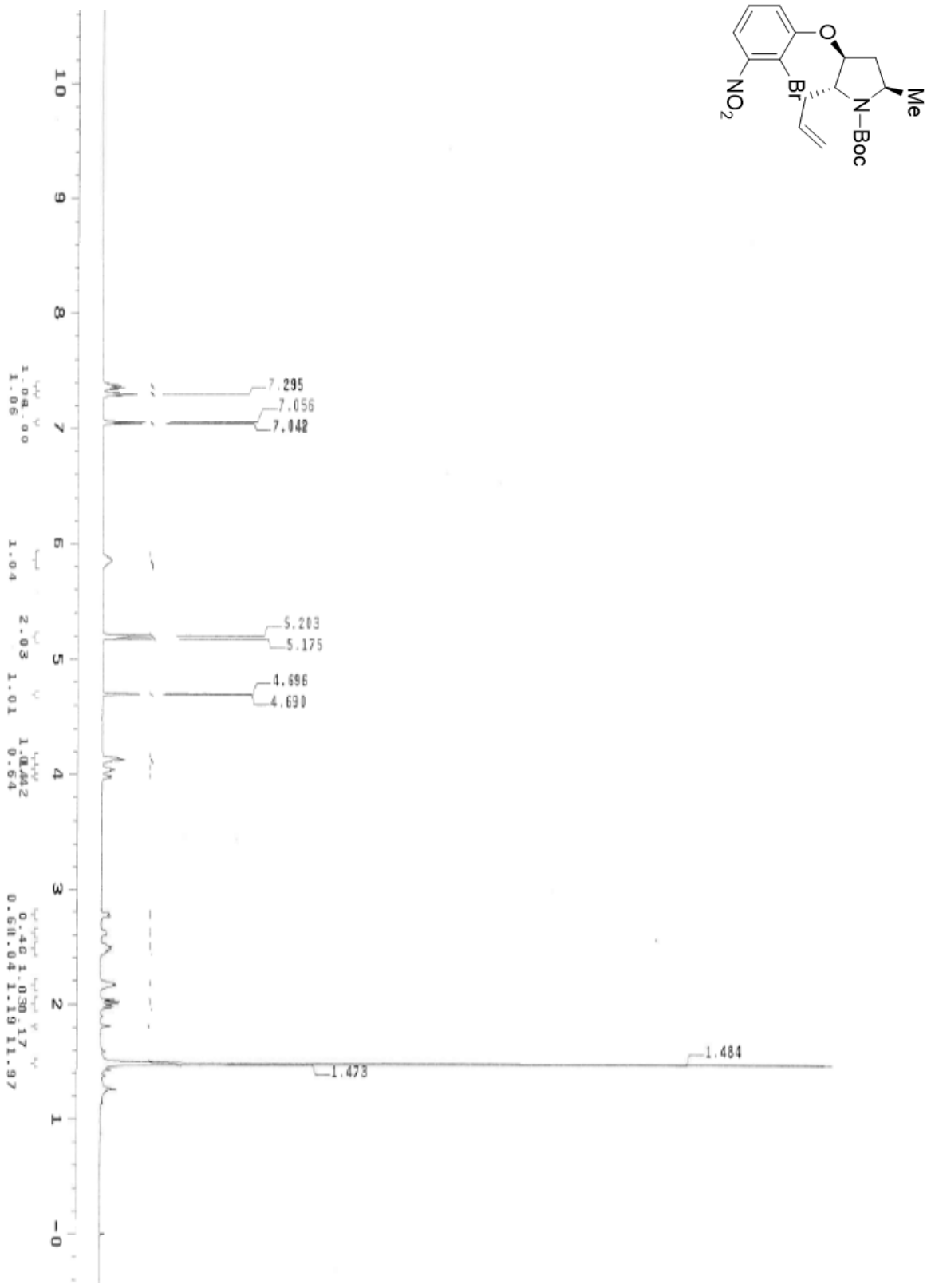

Figure 20: ^{1}H NMR of 2(R)-(2-propen-1-yl)-1-(*t*-butoxycarbonyl)-3(S)-(2-bromo-3-nitrophenoxy-5(R)-methylpyrrolidine **(10)**

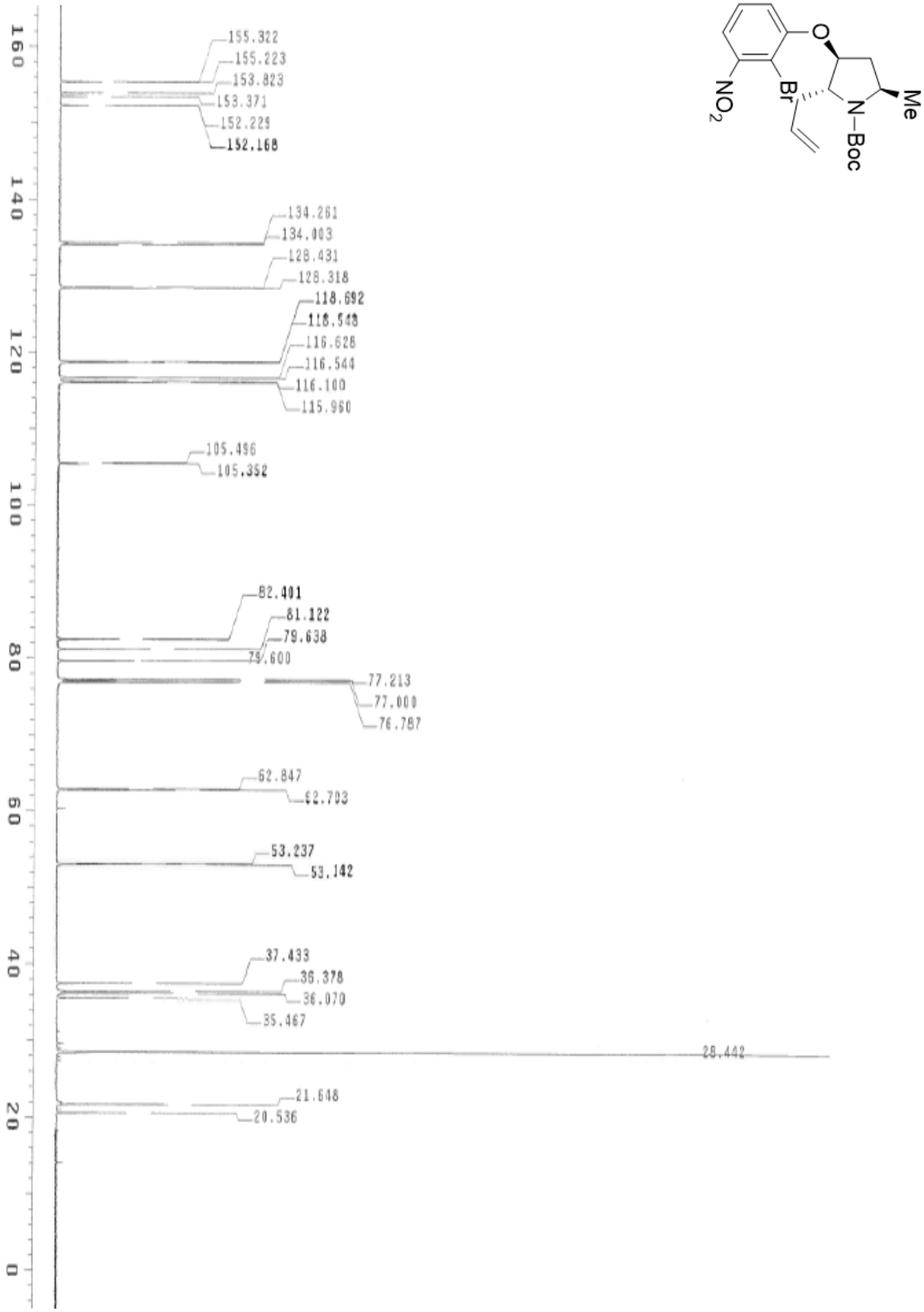

Figure 21: ^{13}C NMR of 2(R)-(2-propen-1-yl)-1-(*t*-butoxycarbonyl)-3(S)-(2-bromo-3-nitrophenoxy-5(R)-methylpyrrolidine **(10)**

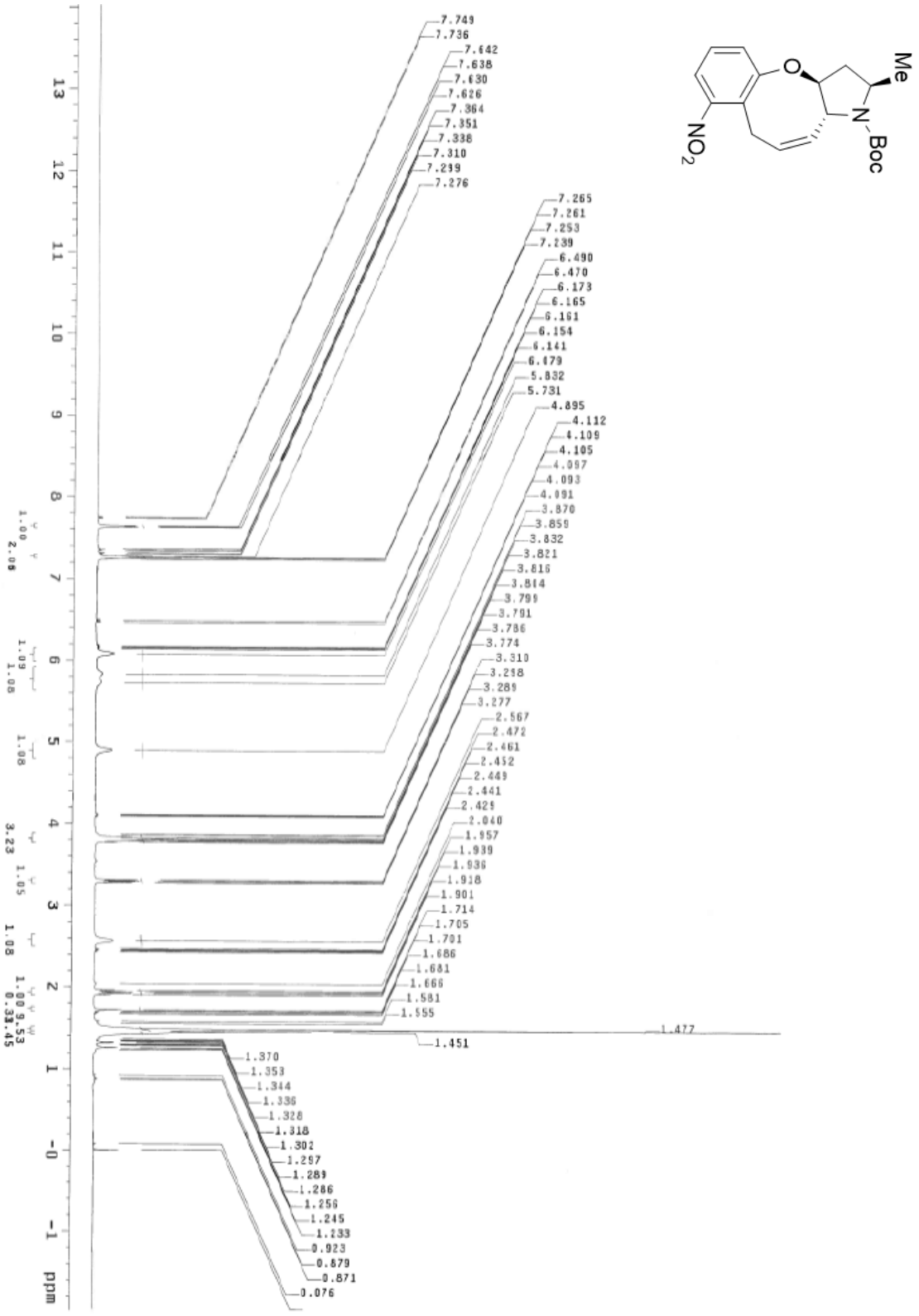

Figure 22: ^{1}H NMR of tricyclic compound **11**

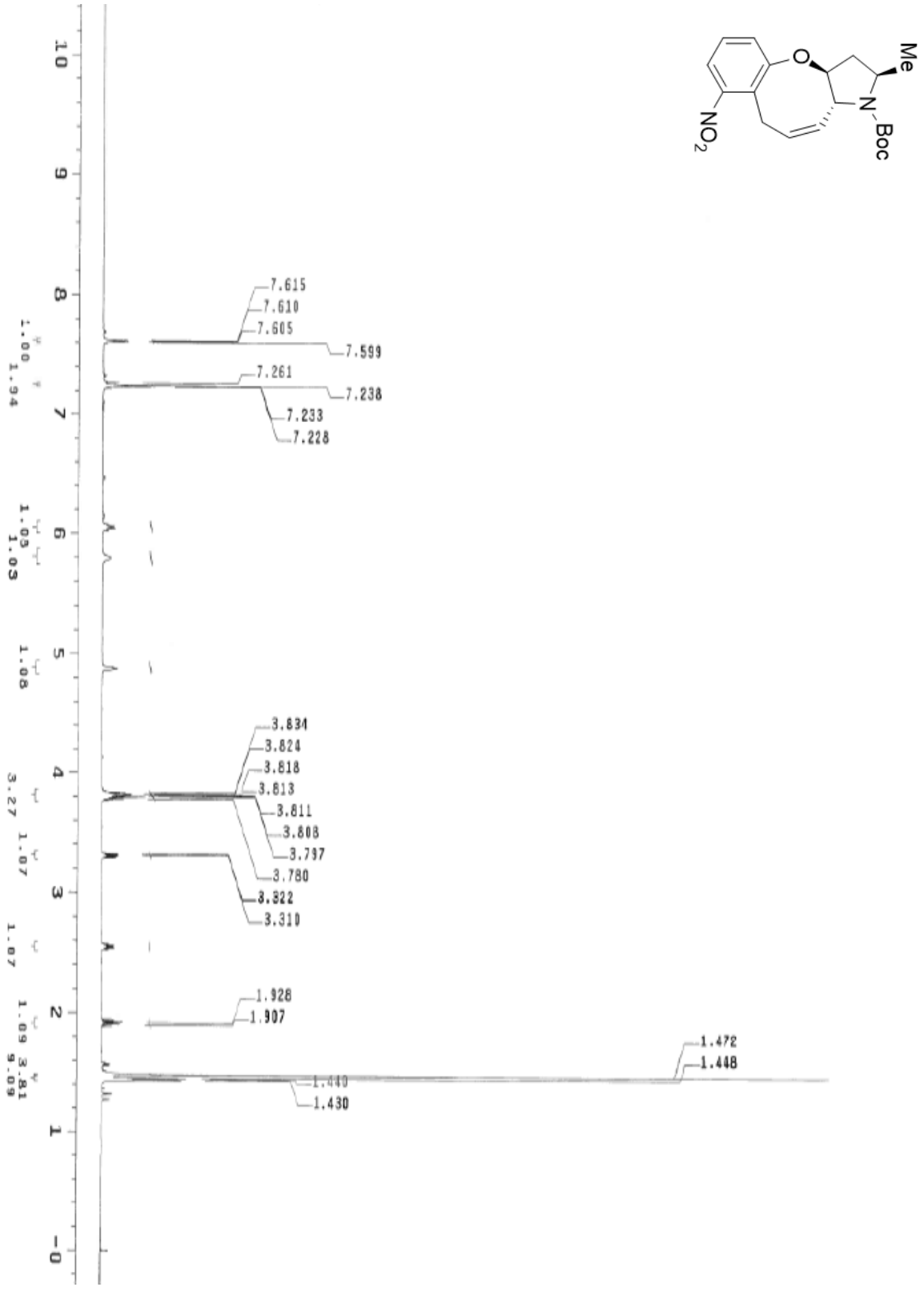

Figure 23: ^{1}H NMR (60 ℃) of tricyclic compound **11**

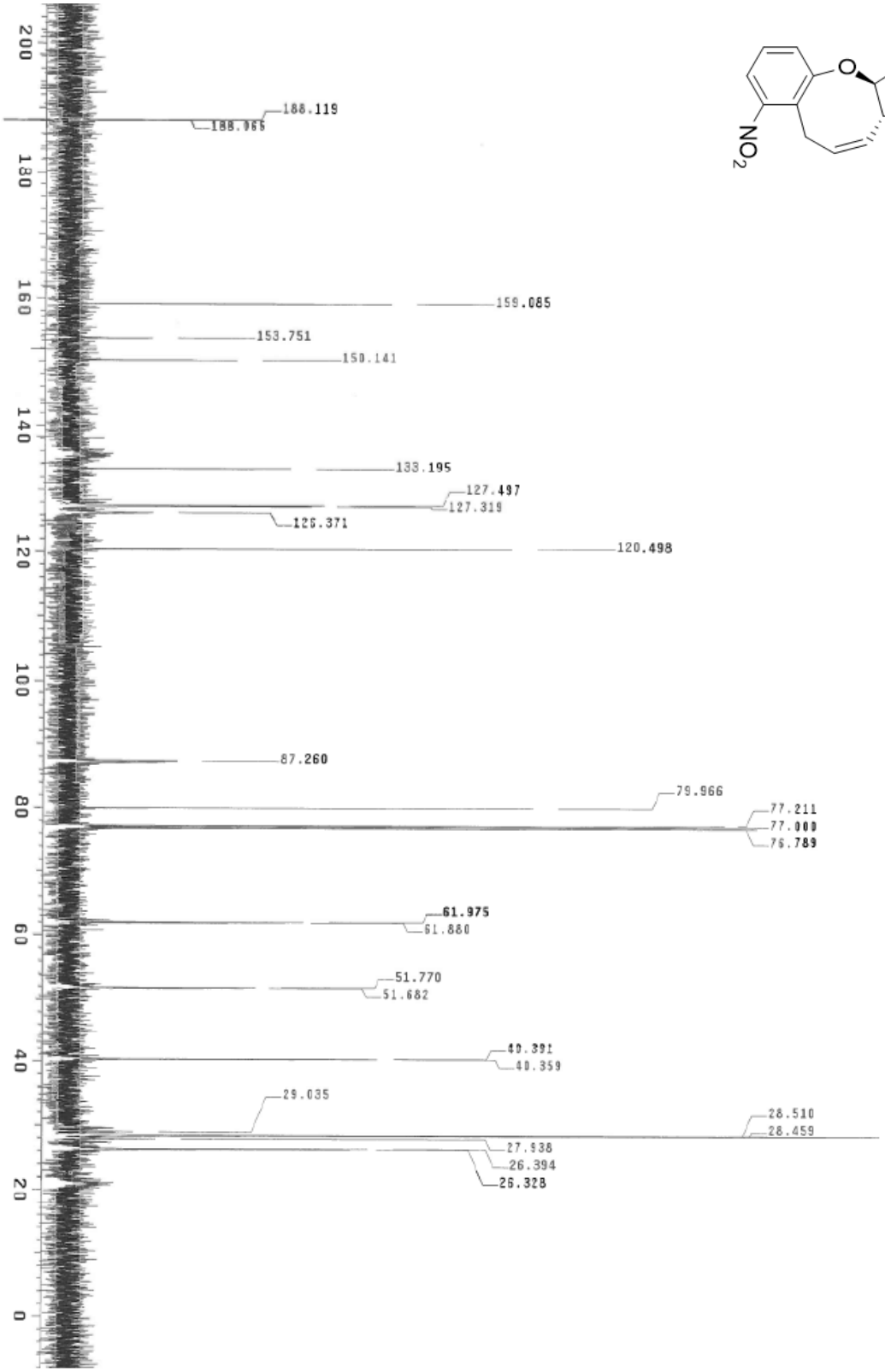

Figure 24: ^{13}C NMR (60 ℃) of tricyclic compound **11**

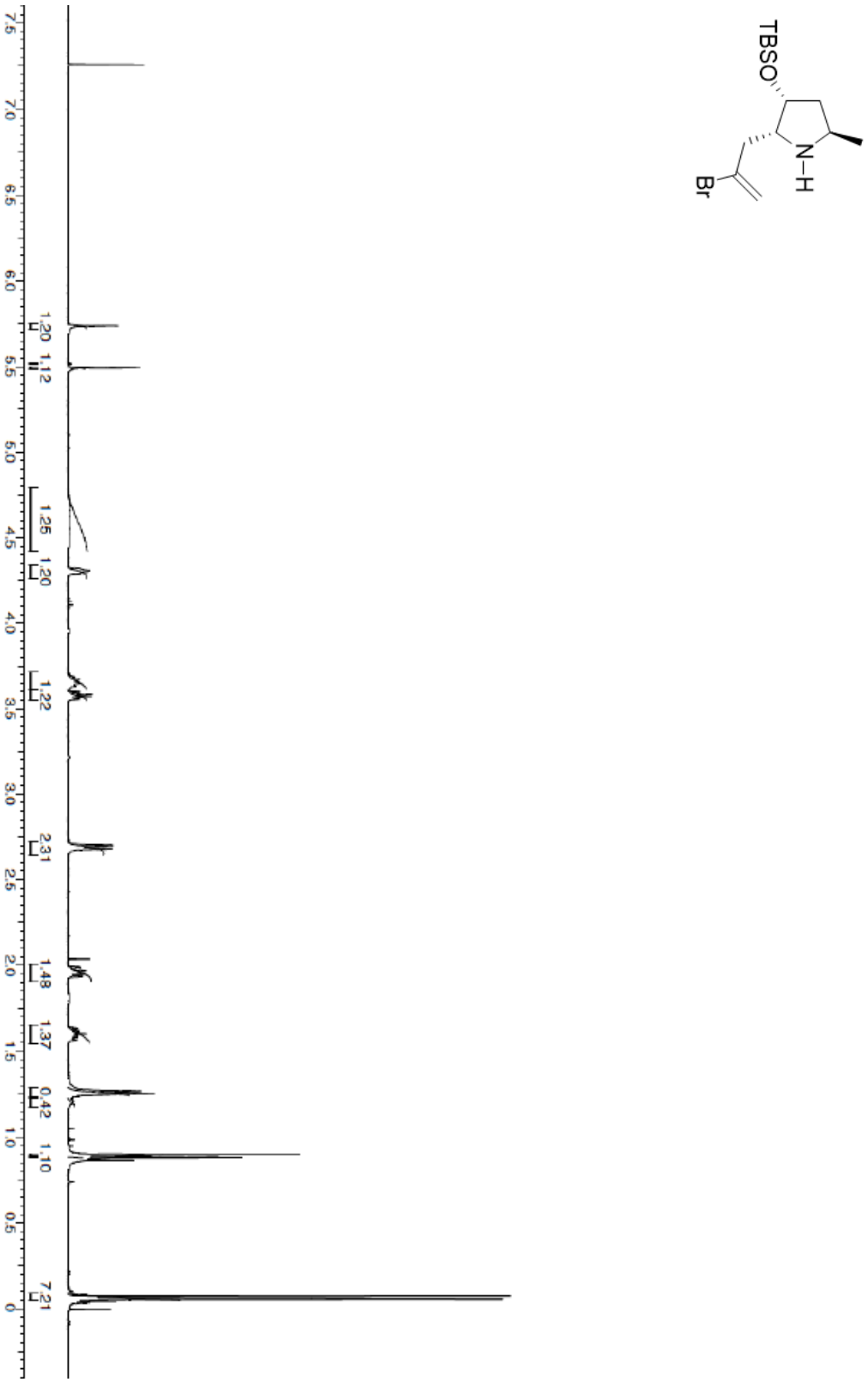

Figure 25: ^{1}H NMR of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-[(*t*-butyldimethylsilyl)-oxy]-5(R)-methylpyrrolidine **(14)**

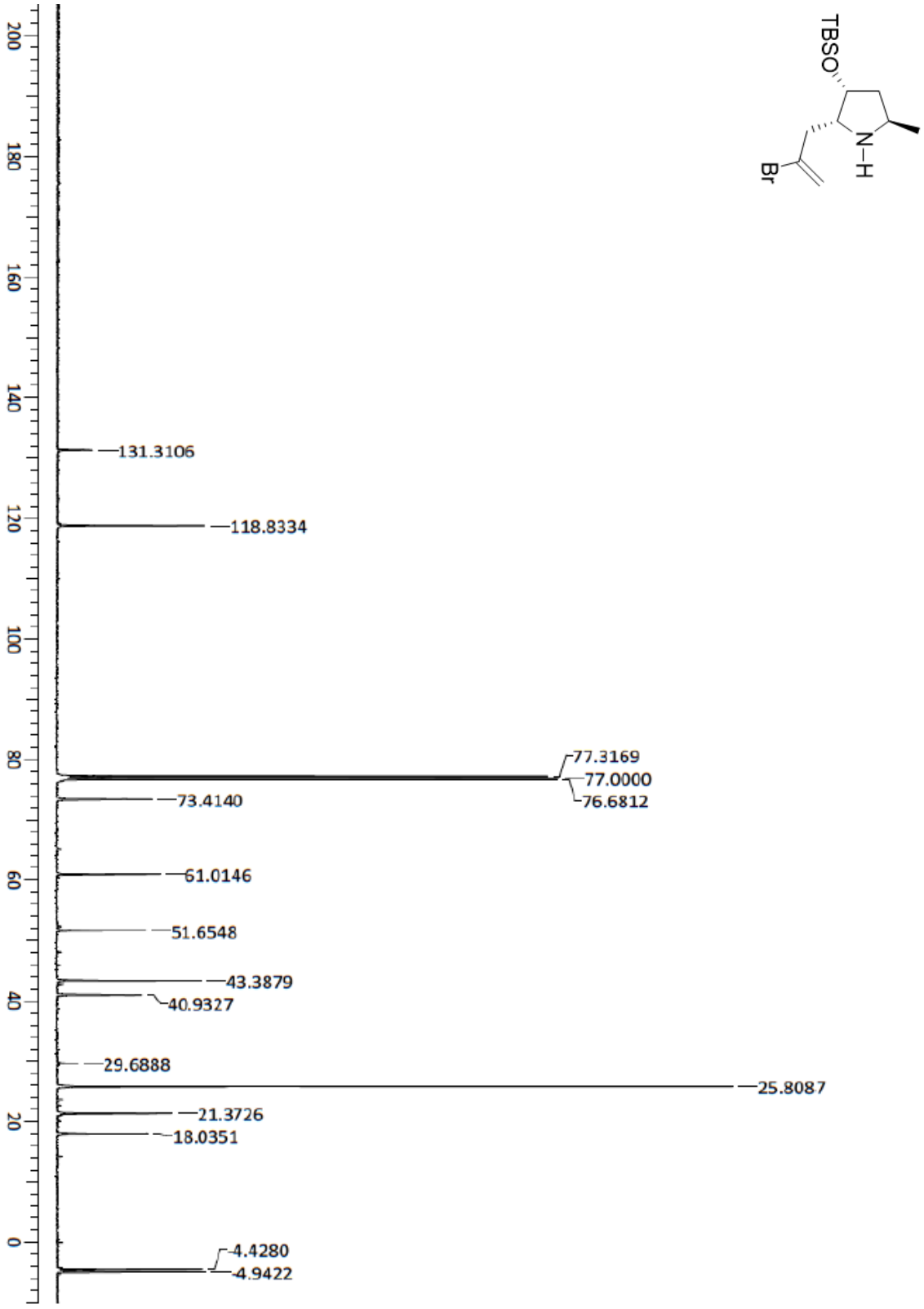

Figure 26: ^{13}C NMR of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-[(*t*-butyldimethylsilyl)-oxy]-5(R)-methylpyrrolidine **(14)**

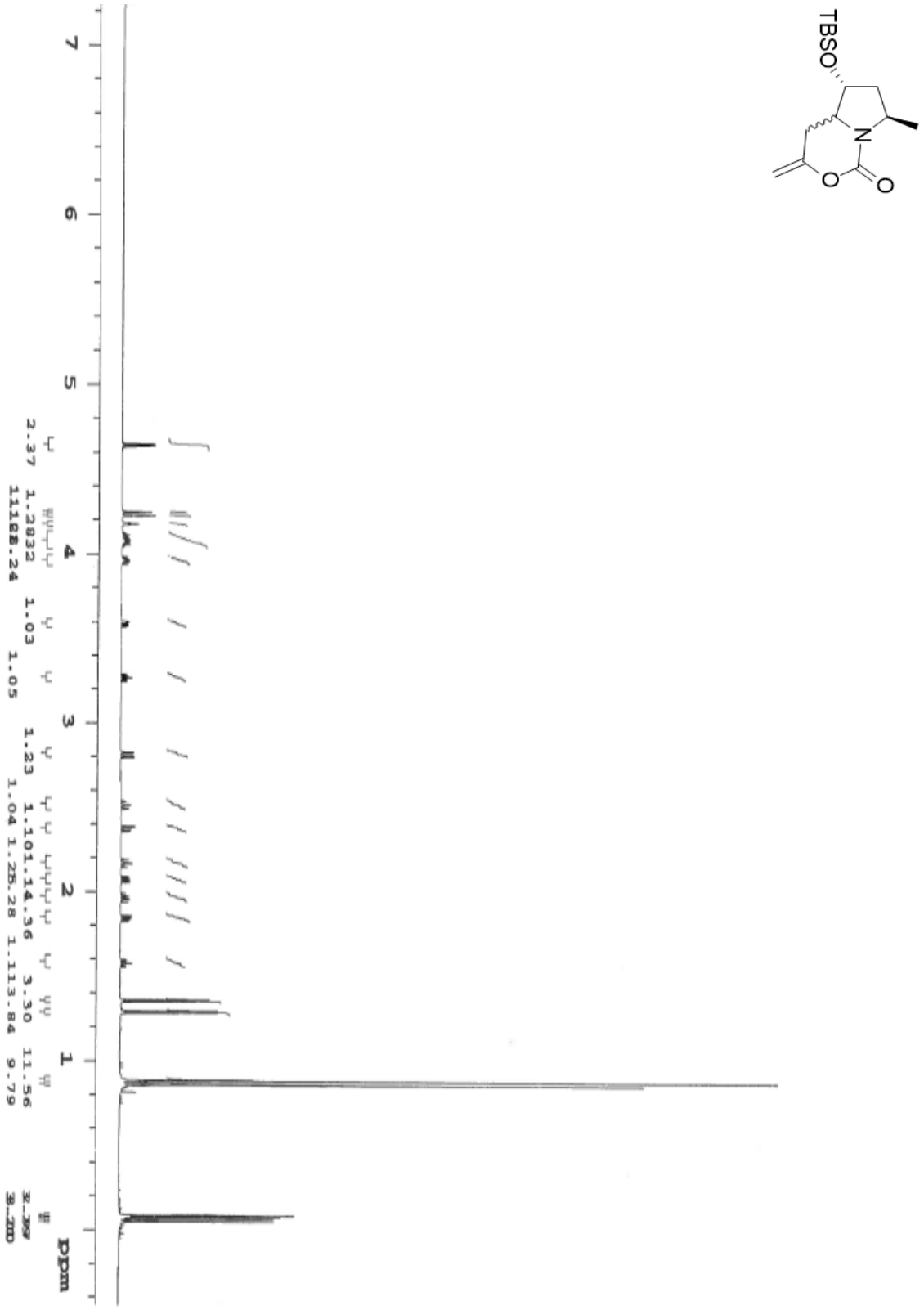

Figure 27: ^{1}H NMR of 5(R)-[(*t*-butyldimethylsilyl)oxy]-(4a)-hexahydro-3-methylene-7(R)-methyl-1H-pyrrolo[1,2-c][1,3]oxazin-1-one **(15)**

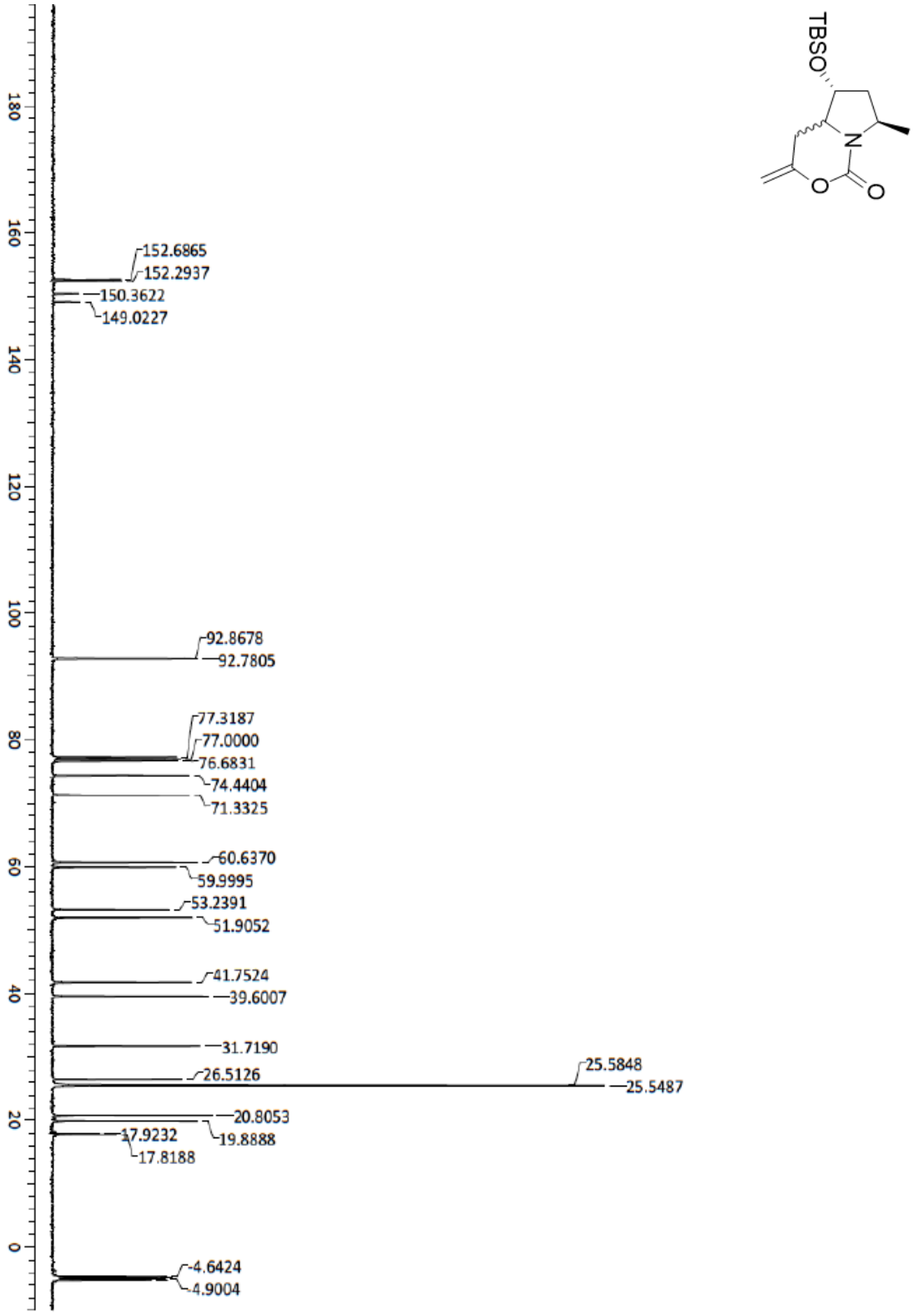

Figure 28: ^{13}C NMR of 5(R)-[(*t*-butyldimethylsilyl)oxy]-(4a)-hexahydro-3-methylene-7(R)-methyl-1H-pyrrolo[1,2-c][1,3]oxazin-1-one **(15)**

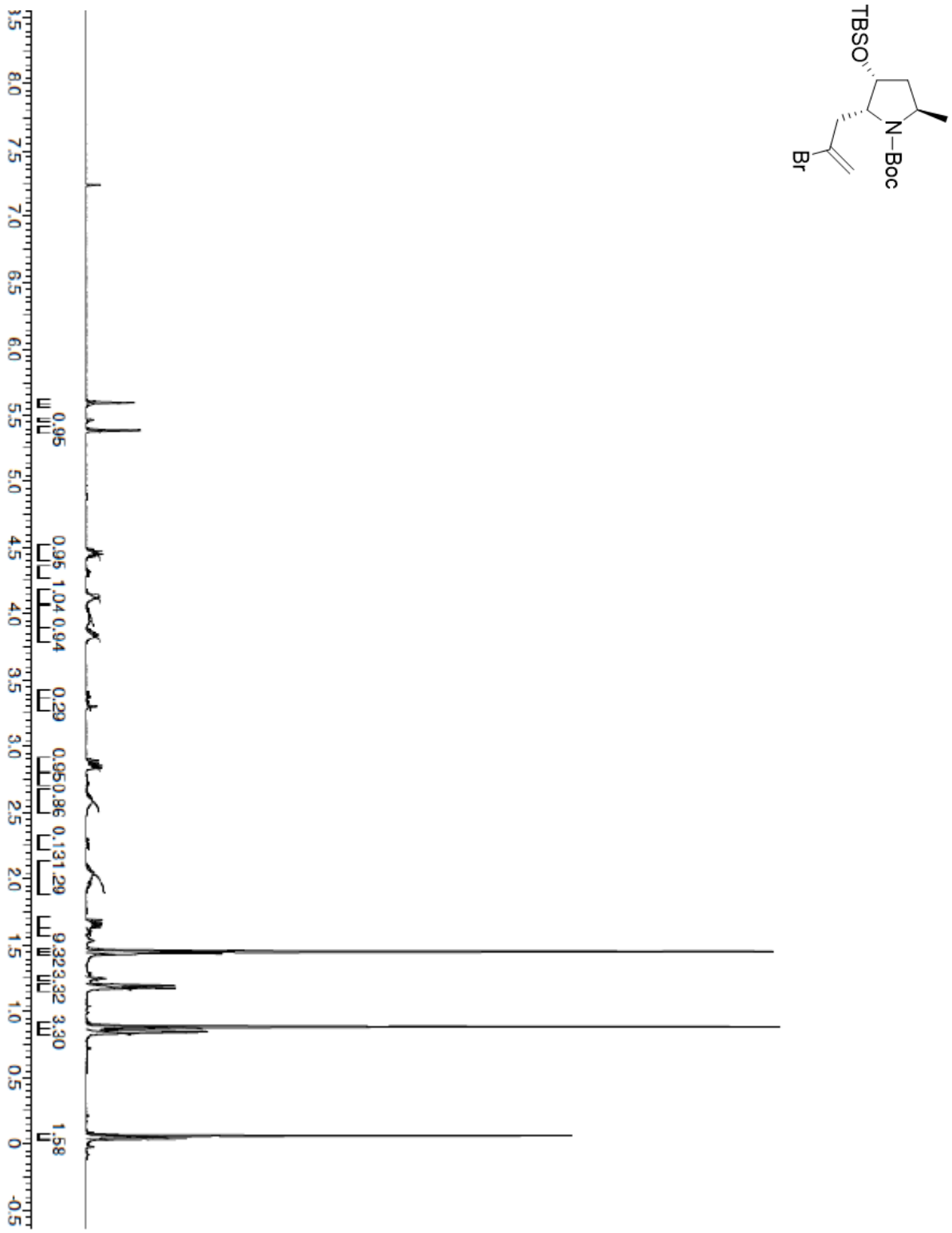

Figure 29: ^{1}H NMR of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-[(*t*-butyldimethylsilyl)-oxy]-1-(*t*-butoxycarbonyl)-5(R)-methyl-pyrrolidine **(16)**

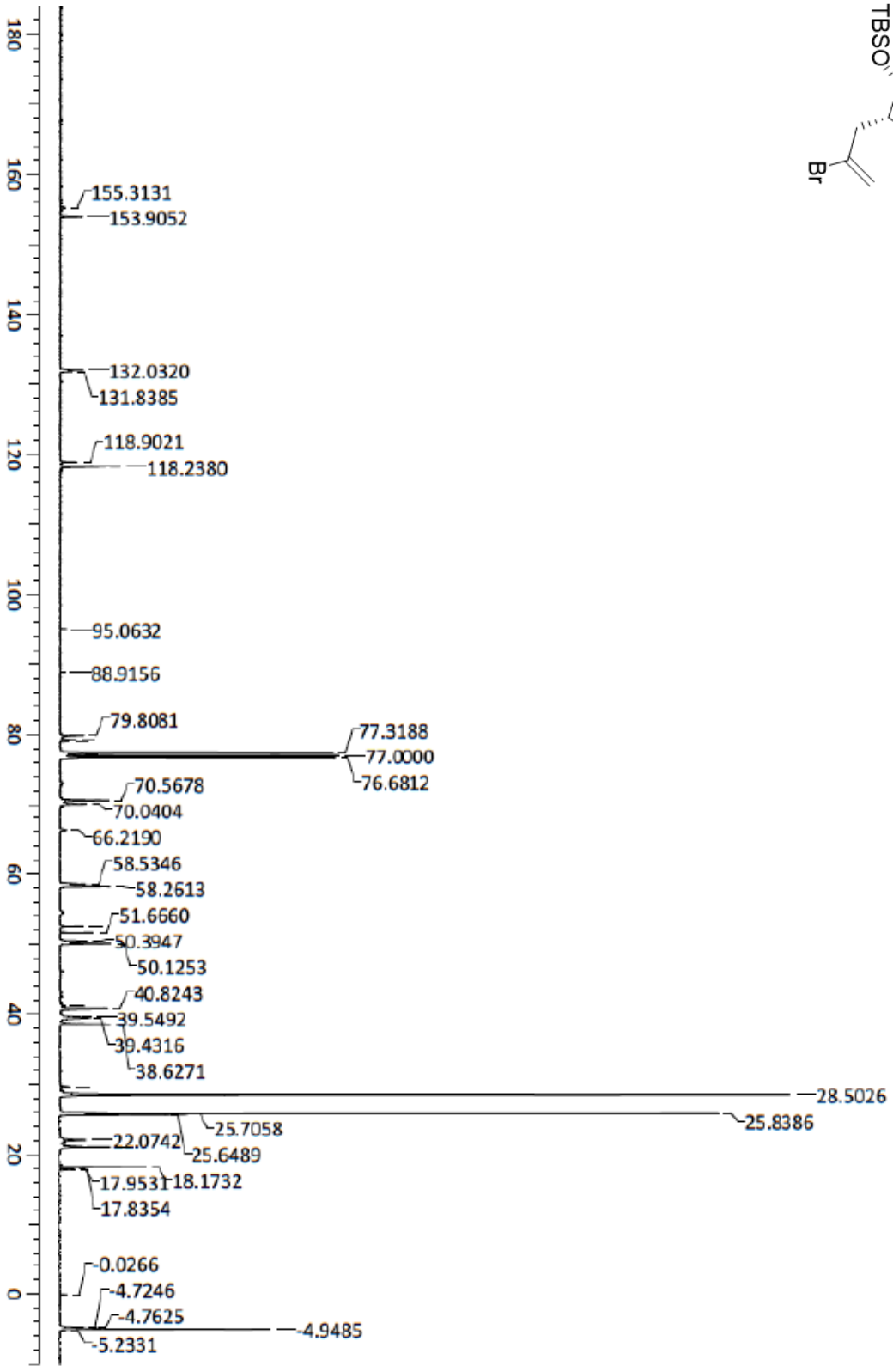

Figure 30: ^{13}C NMR (65 ℃) of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-[(*t*-butyldimethylsilyl)-oxy]-1-(*t*-butoxycarbonyl)-5(R)-methyl-pyrrolidine **(16)**

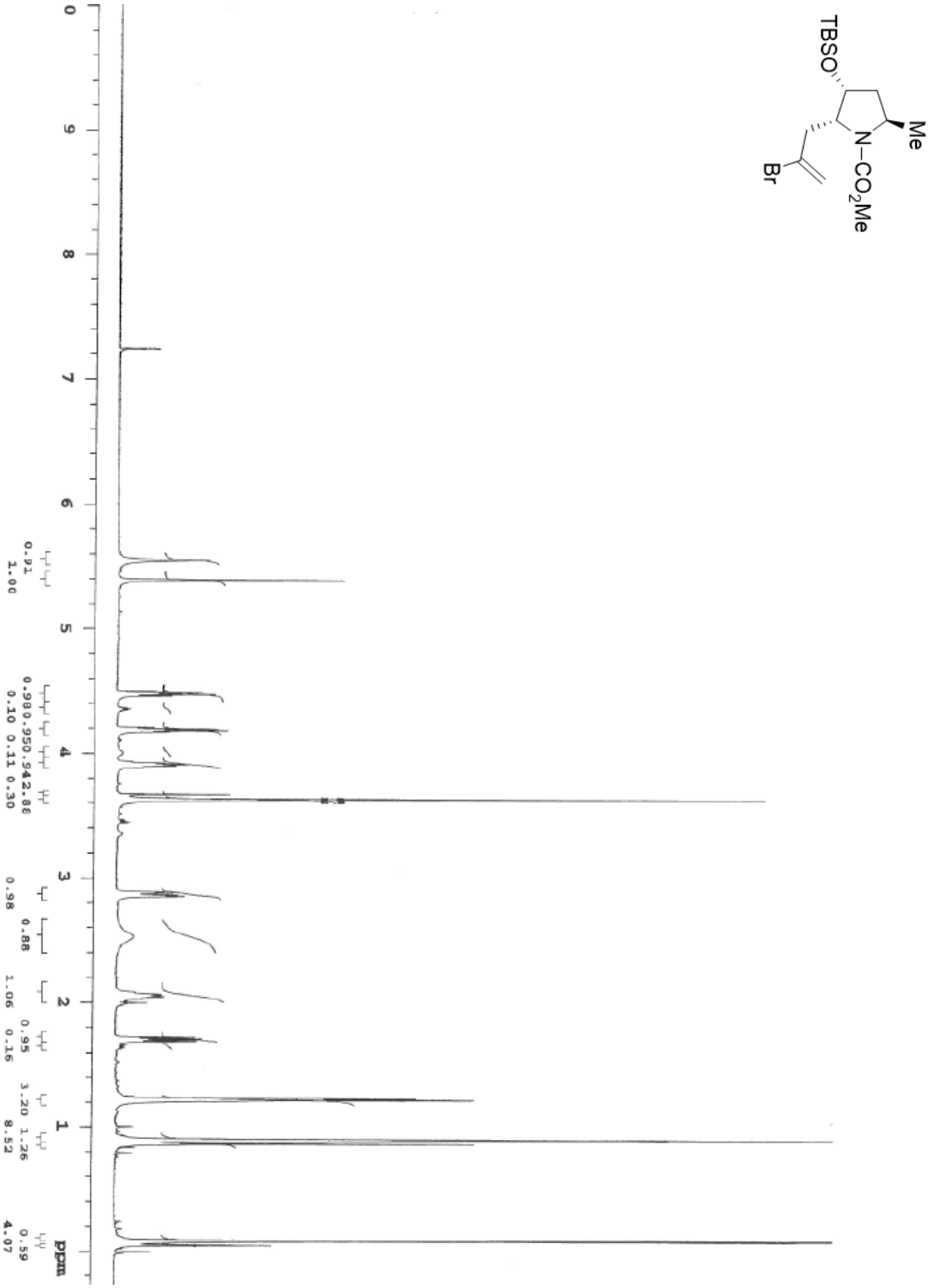

Figure 31: ^{1}H NMR (65 ℃) of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-[(*t*-butyldimethylsilyl)-oxy]-1-(methoxycarbonyl)-5(R)-methylpyrrolidine **(17)**

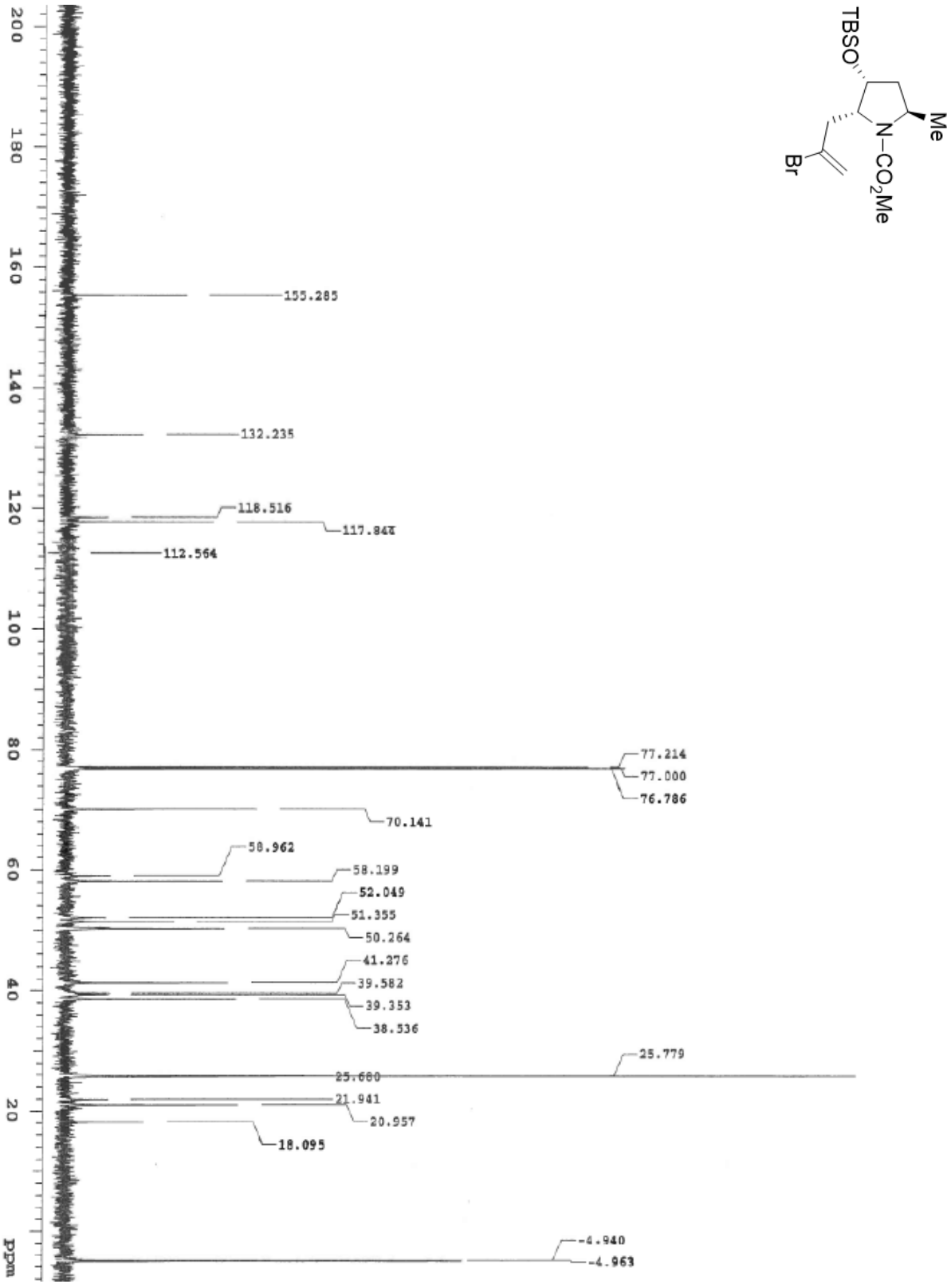

Figure 32: ^{13}C NMR (65 ℃) of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-[(*t*-butyldimethylsilyl)-oxy]-1-(methoxycarbonyl)-5(R)-methylpyrrolidine **(17)**

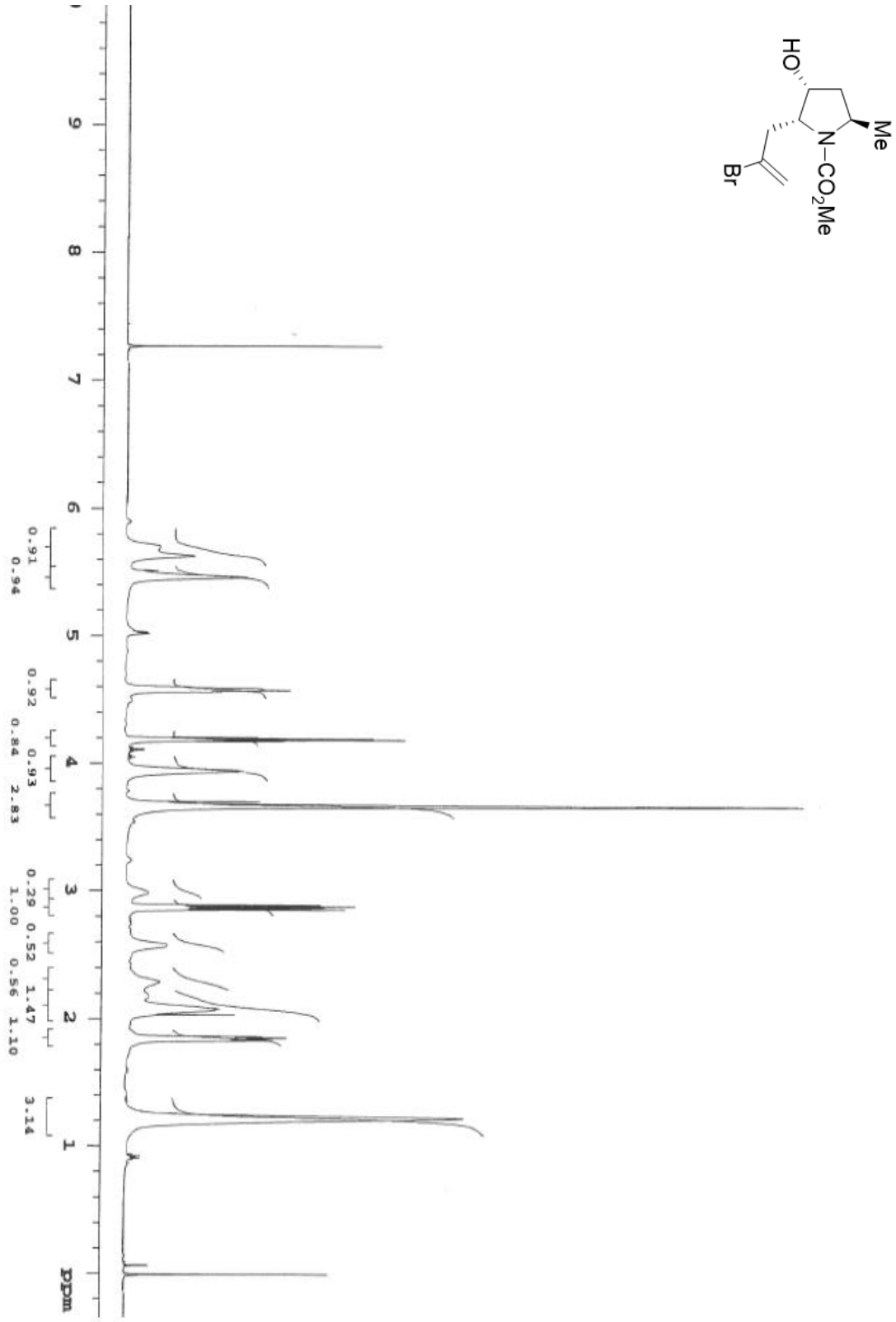

Figure 33: ^{1}H NMR of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)-5(R)-methylpyrrolidine **(18)**

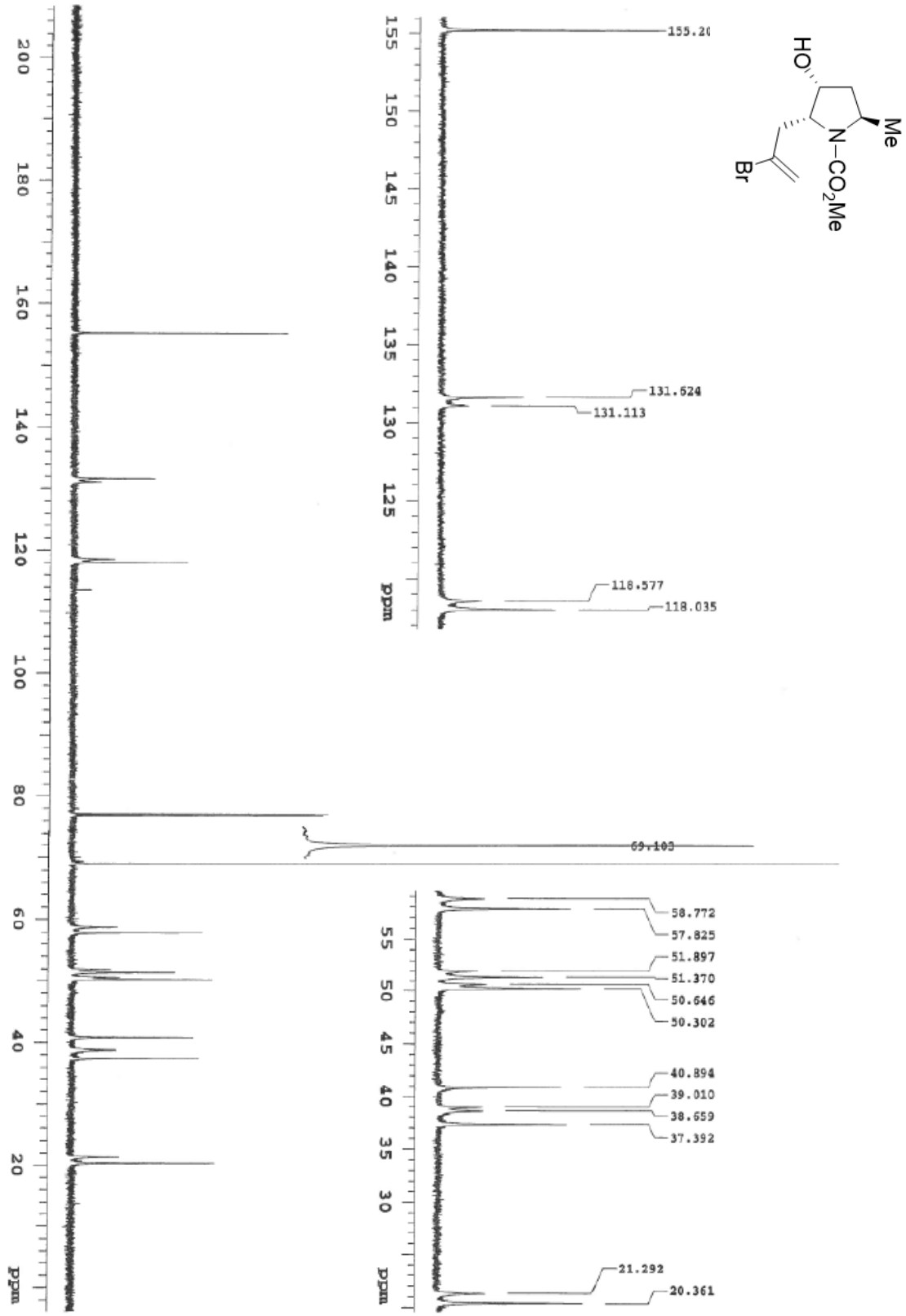

Figure 34: ^{13}C NMR of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)-5(R)-methylpyrrolidine **(18)**

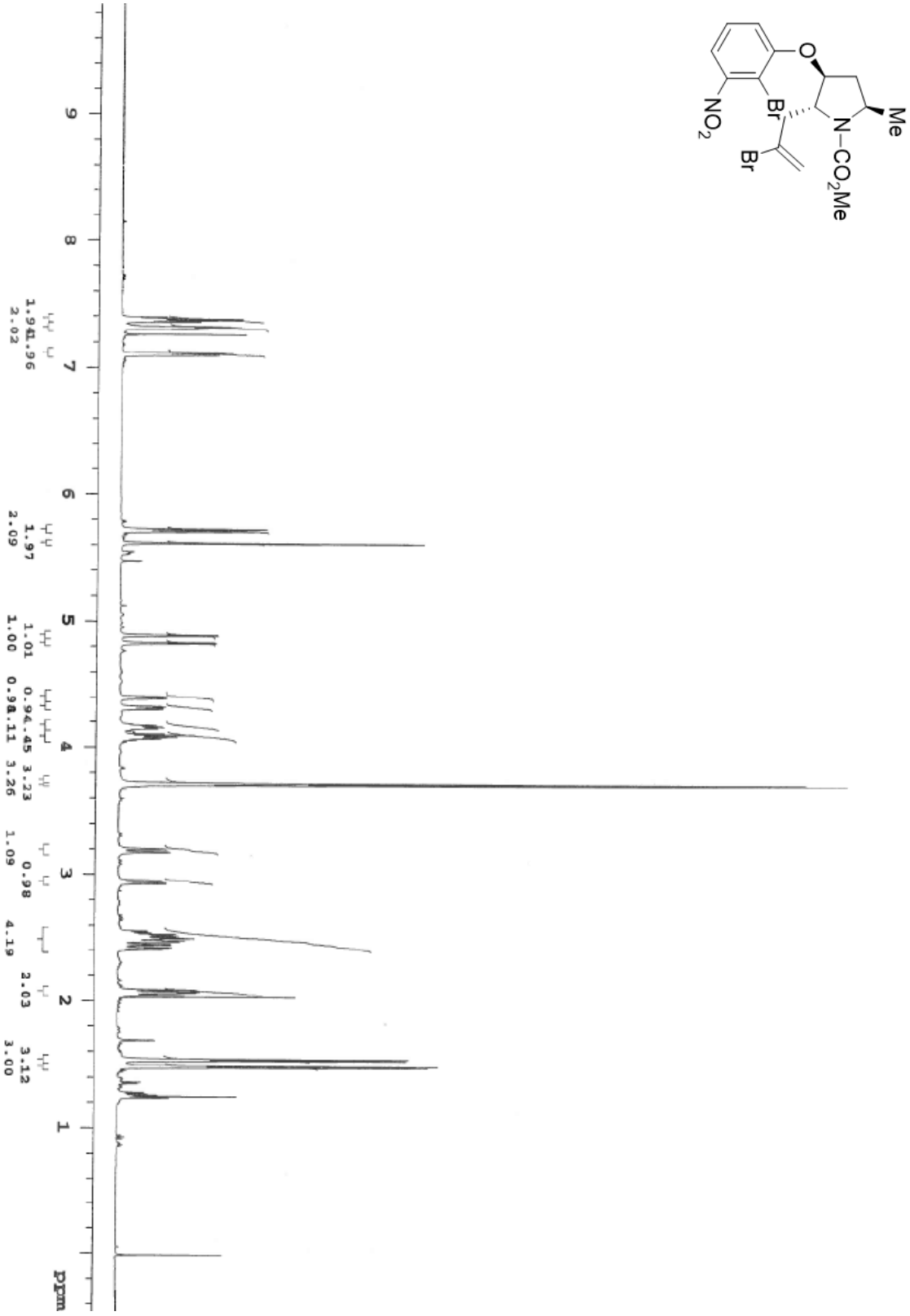

Figure 35: ^{1}H NMR of 3(S)-(2-bromo-3-nitrophenoxy)-2(R)-(2-bromo-propen-1-yl)-1-(methoxycarbonyl)-5(R)-methylpyrrolidine **(19)**

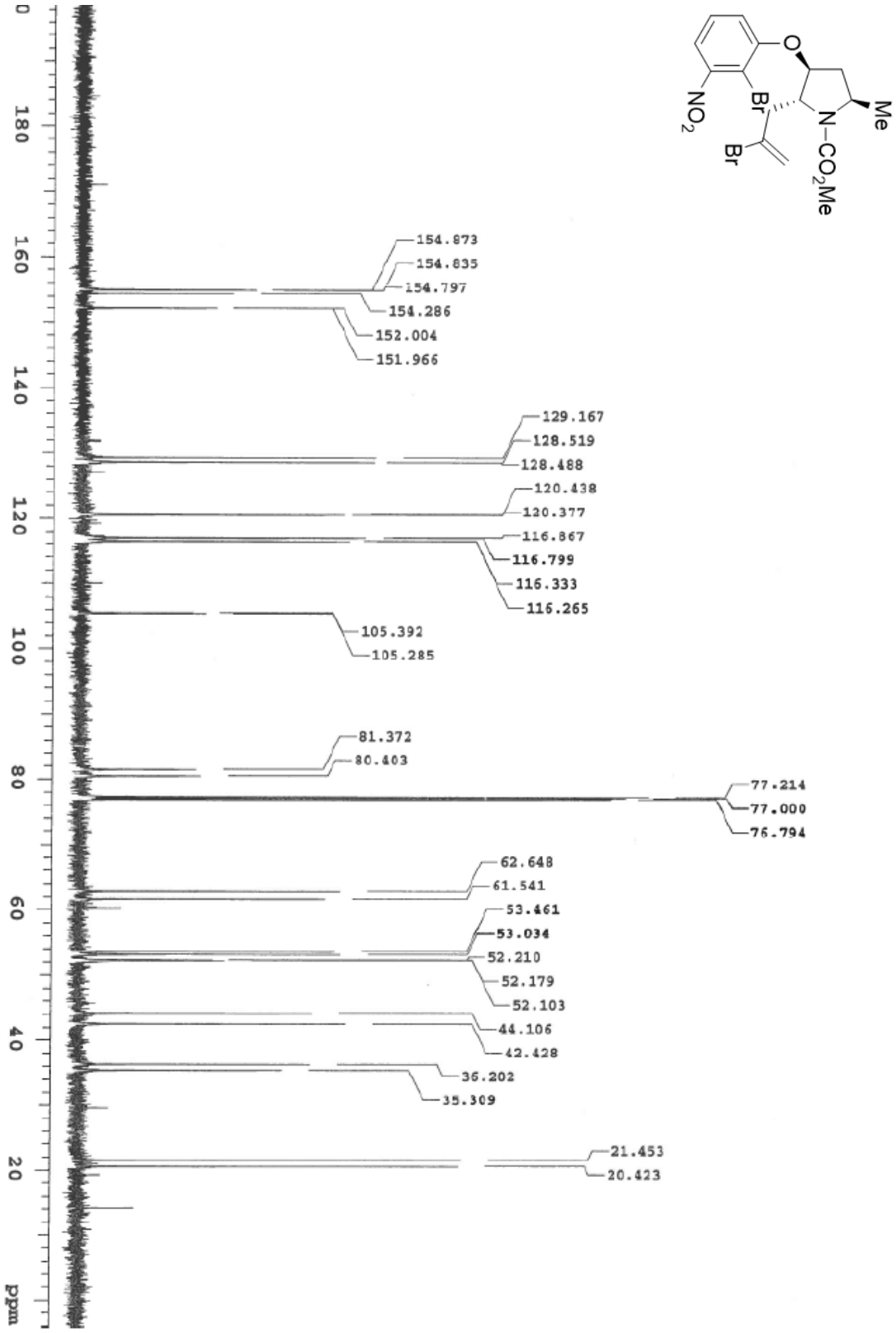

Figure 36: ^{13}C NMR of 3(S)-(2-bromo-3-nitrophenoxy)-2(R)-(2-bromo-propen-1-yl)-1-(methoxycarbonyl)-5(R)-methylpyrrolidine **(19)**

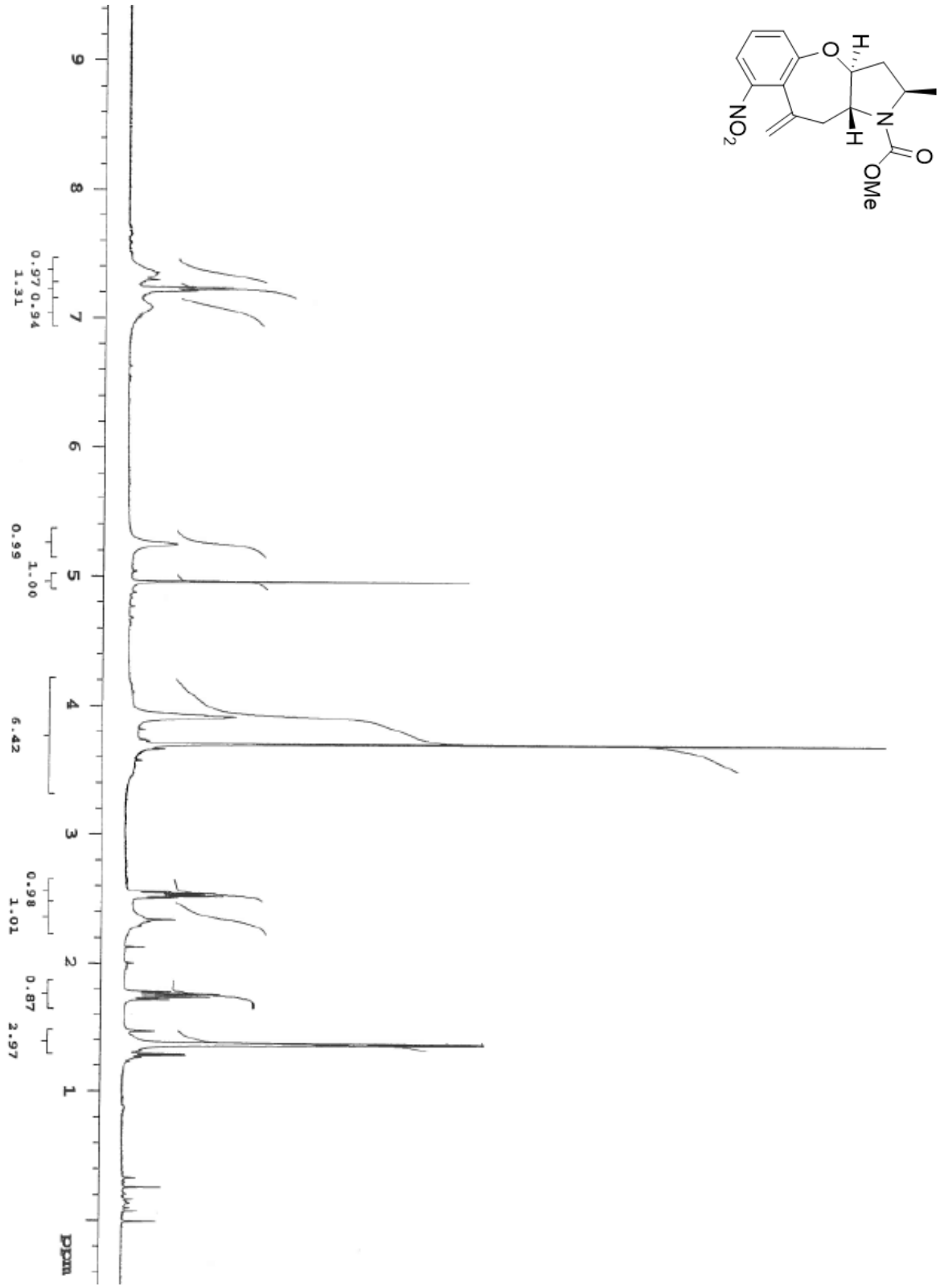

Figure 37: ^{1}H NMR (65 ℃) of tricyclic Compound **20**

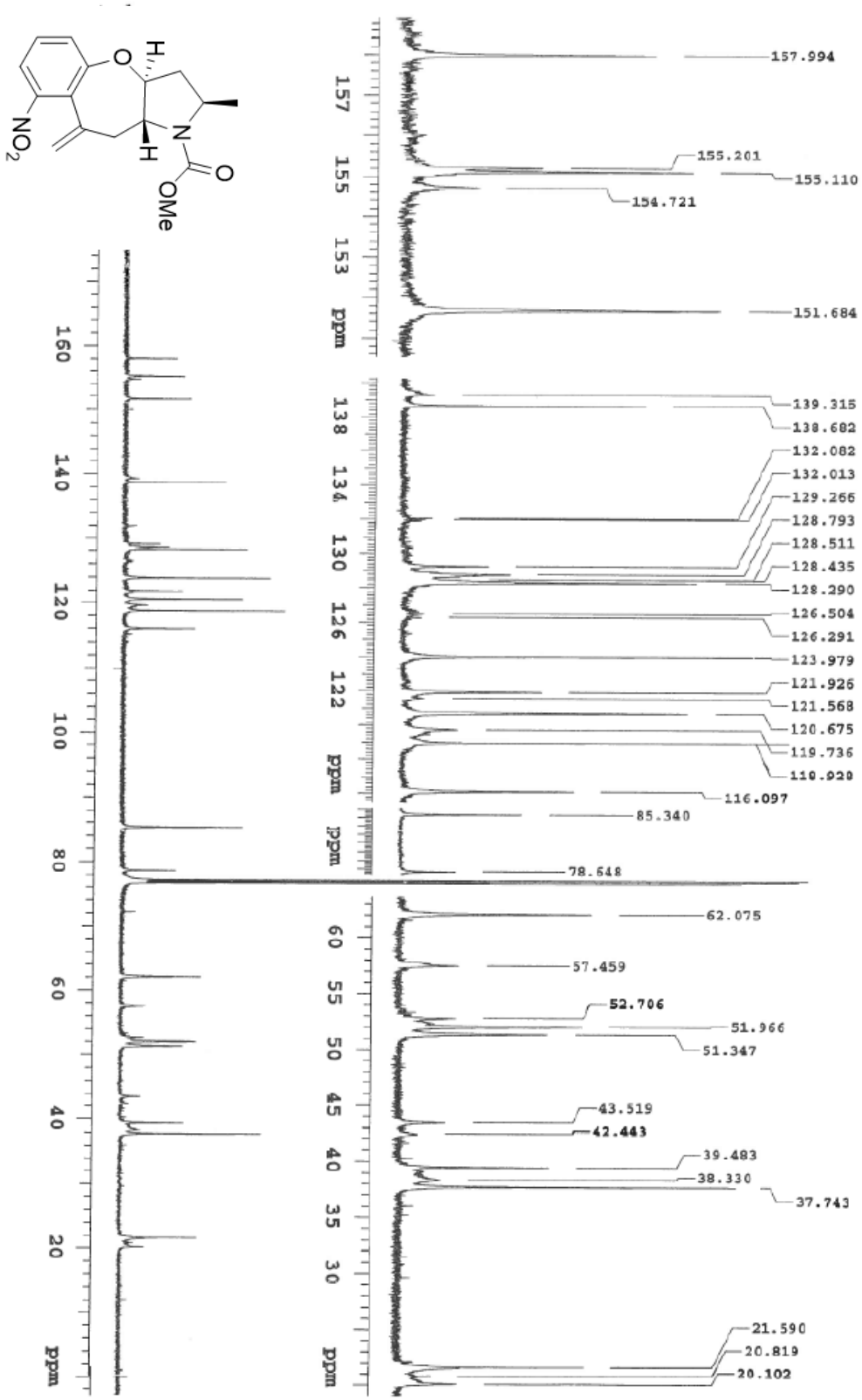

Figure 38: ^{13}C NMR of (65 ℃) of tricyclic Compound **20**

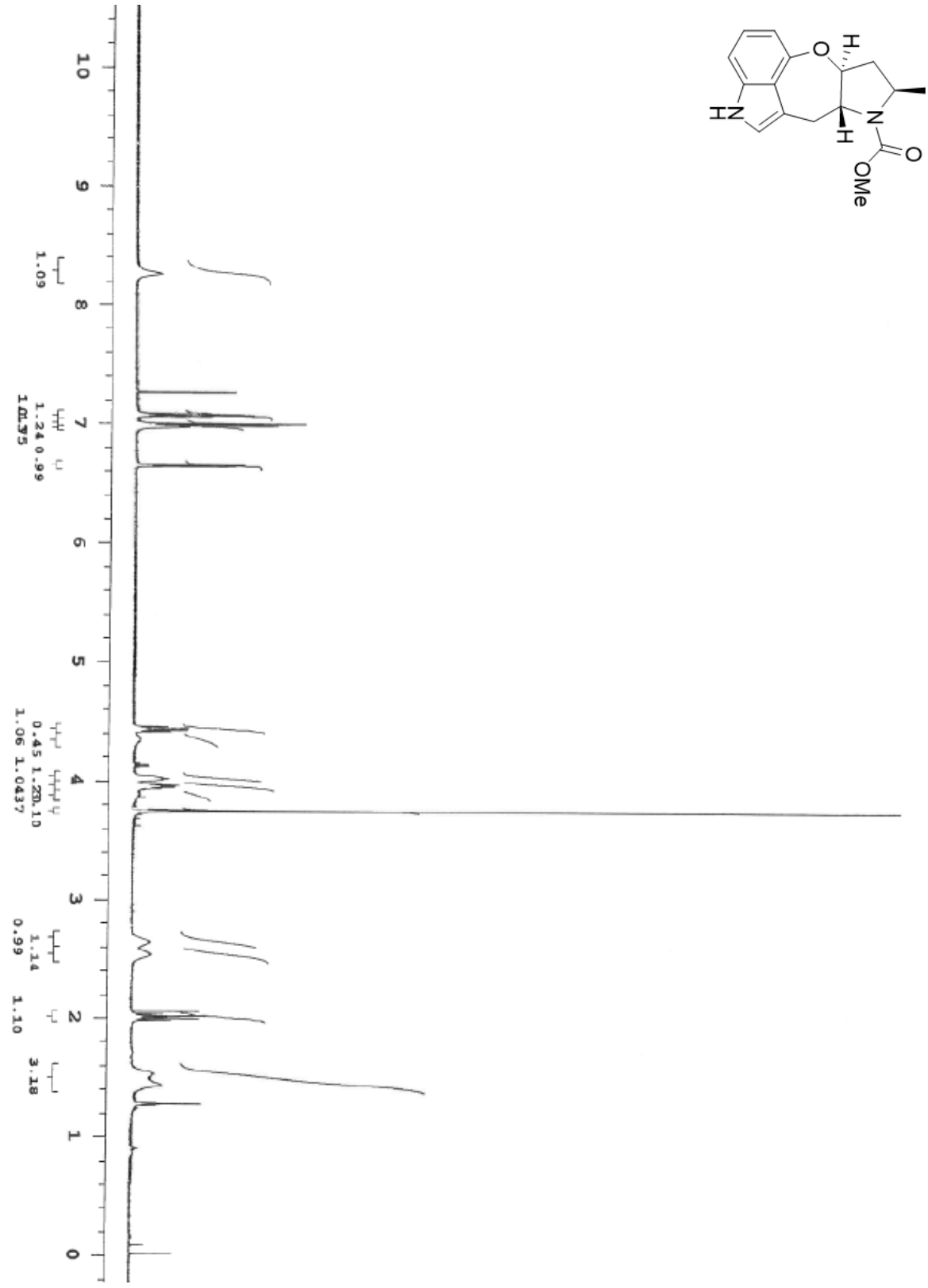

Figure 39: ^{1}H NMR of (6aR,8R,9aS)-7-methoxycarbonyl-6,6a,7,8,9,9a-hexahydro-8-methyl-H-pyrrolo[2′,3′:6,7]oxepino[4,3,2-cd]indole **(21)**

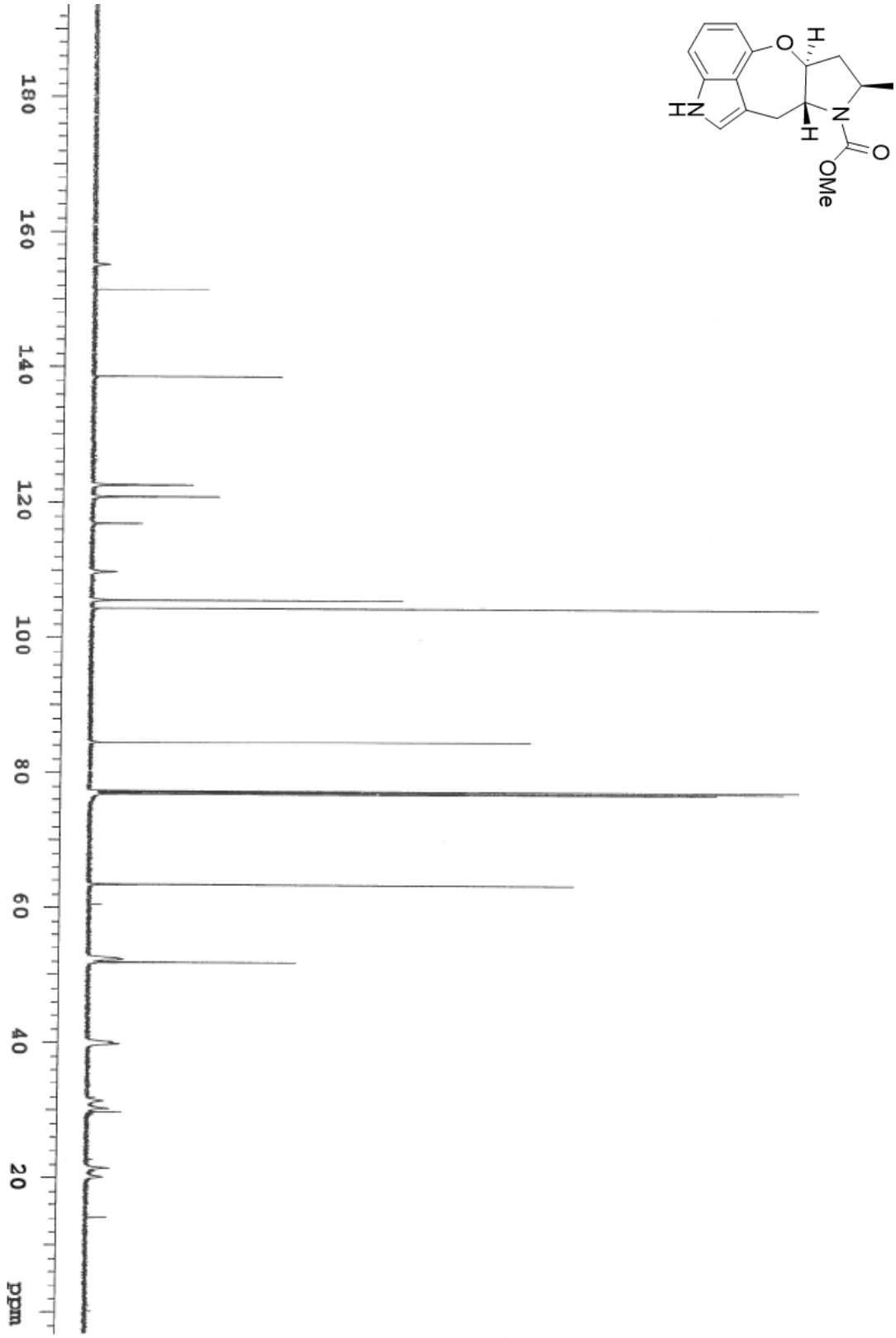

Figure 40: ^{13}C NMR of (6aR,8R,9aS)-7-methoxycarbonyl-6,6a,7,8,9,9a-hexahydro-8-methyl-H-pyrrolo[2′,3′:6,7]oxepino[4,3,2-cd]indole **(21)**

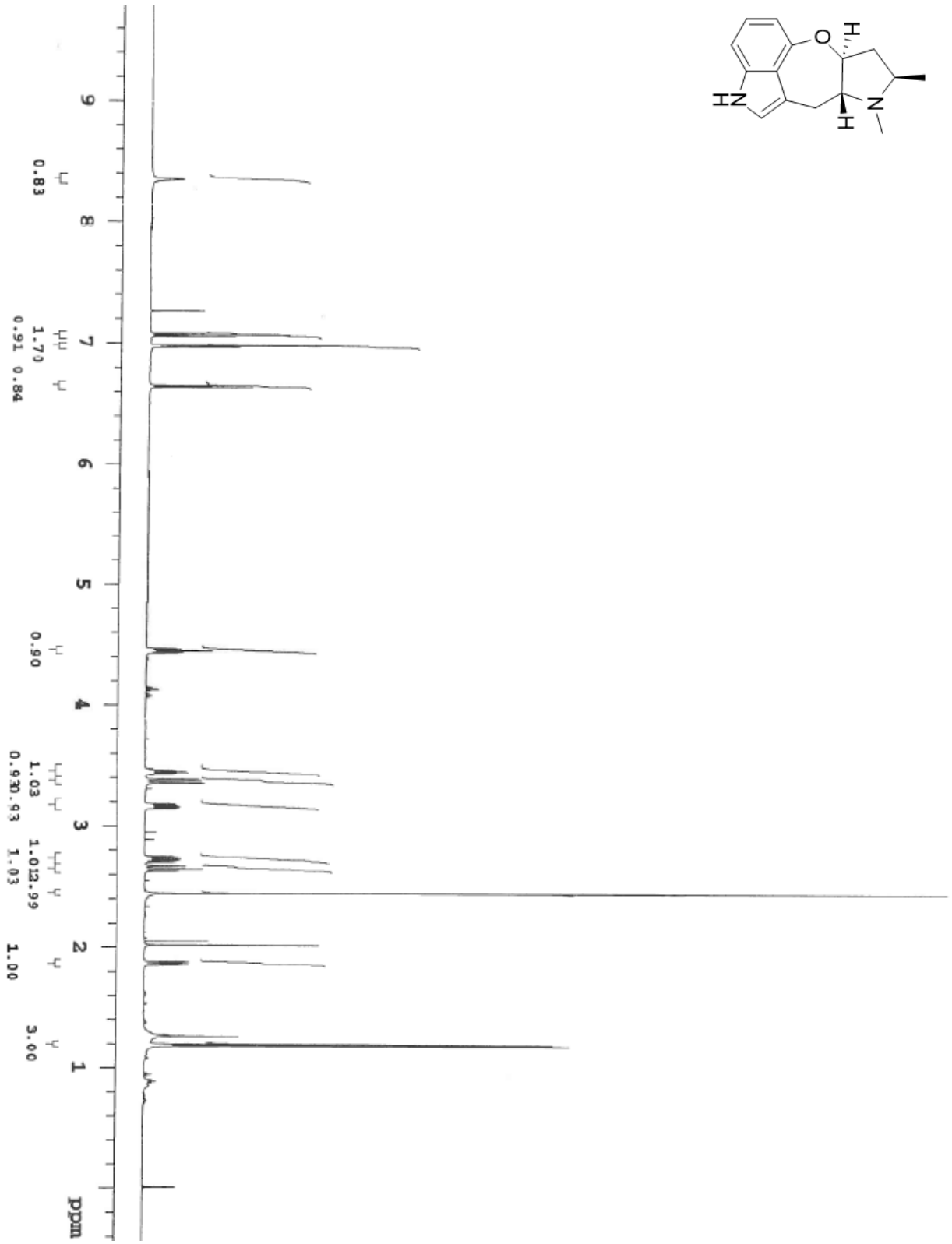

Figure 41: ^{1}H NMR of ht-13-B

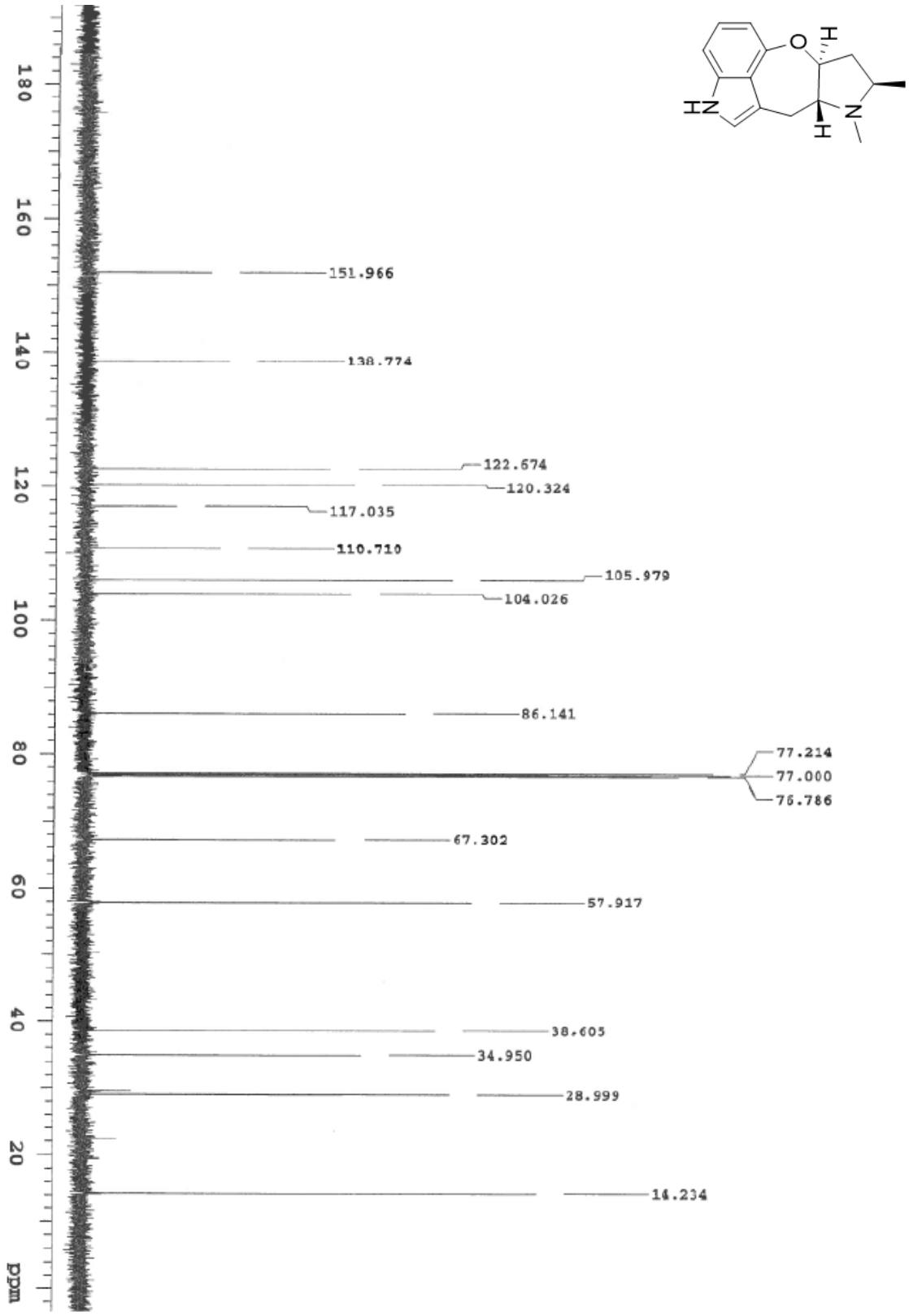

Figure 42: ^{13}C NMR of ht-13-B

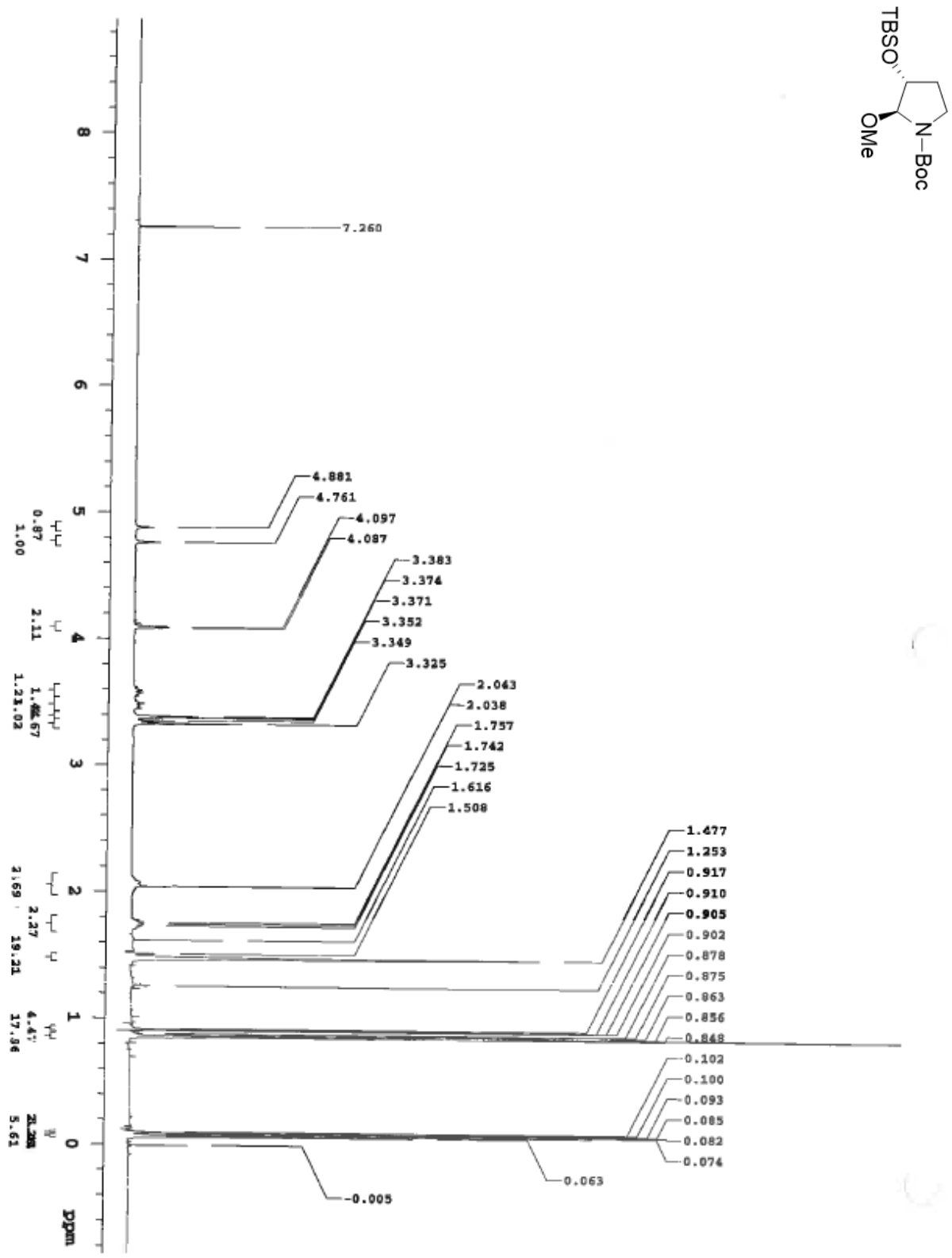

Figure 43: ^{1}H NMR of 3-(*t*-butyl-dimethyl-silanyloxy)-2-methoxy-pyrrolidine-1-carboxylic acid *t*-butyl ester **(28)**

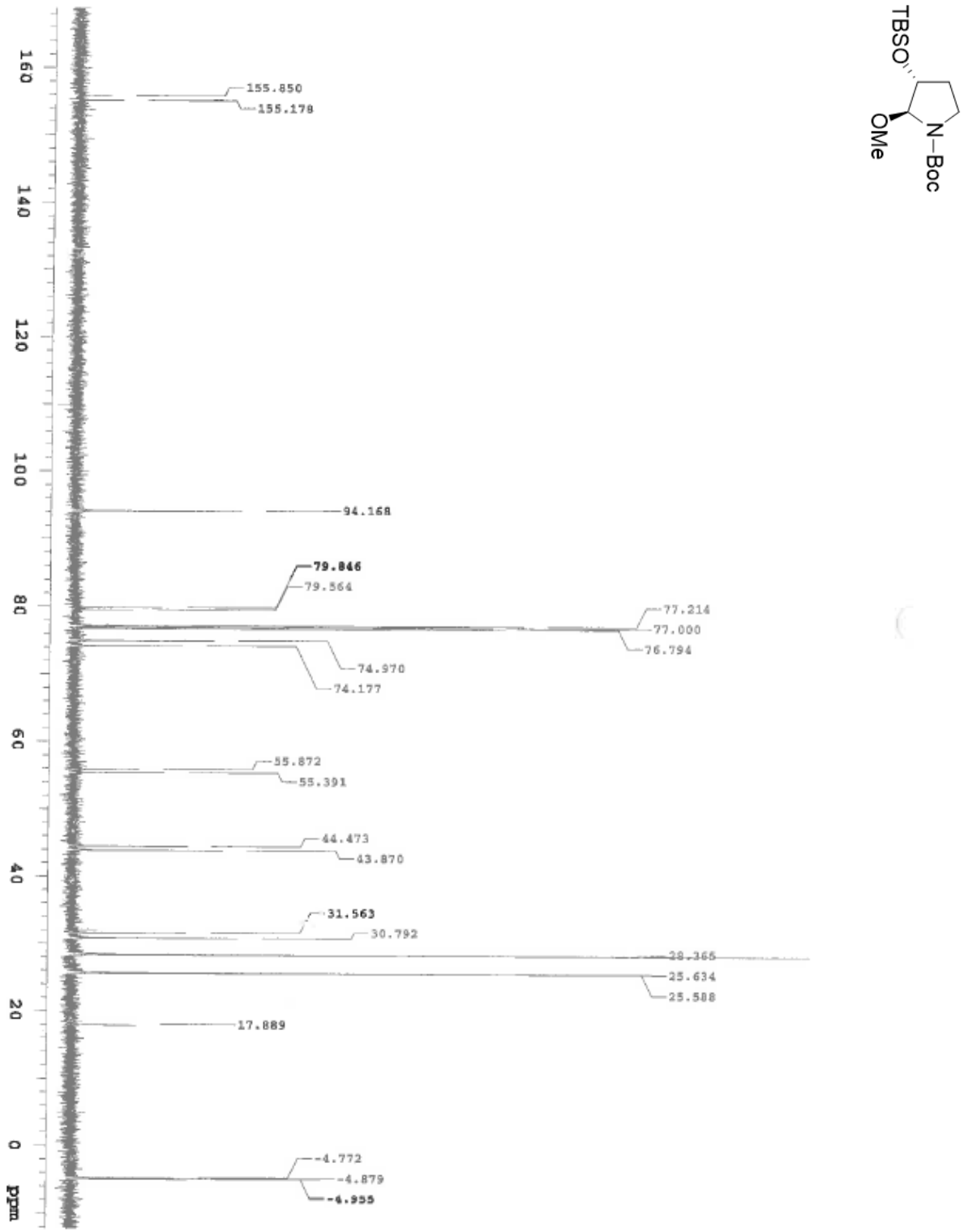

Figure 44: ^{13}C NMR of 3-(*t*-butyl-dimethyl-silanyloxy)-2-methoxy-pyrrolidine-1-carboxylic acid *t*-butyl ester **(28)**

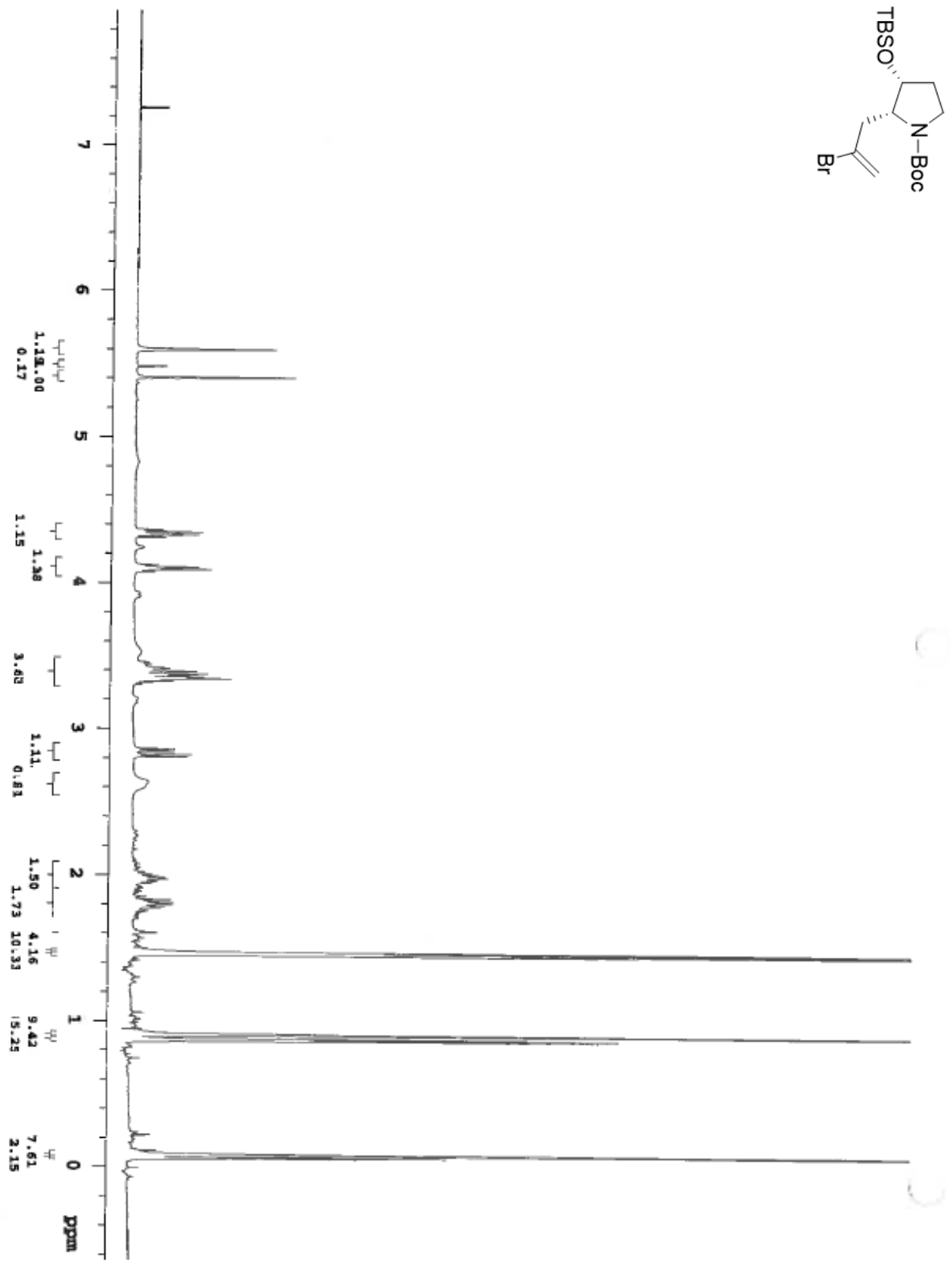

Figure 45: ^{1}H NMR (65 ℃) of 2-(2-bromo-allyl)-3-(*t*-butyl-dimethyl-silanyloxy)-pyrrolidine-1-carboxylic acid *t*-butyl ester **(29)**

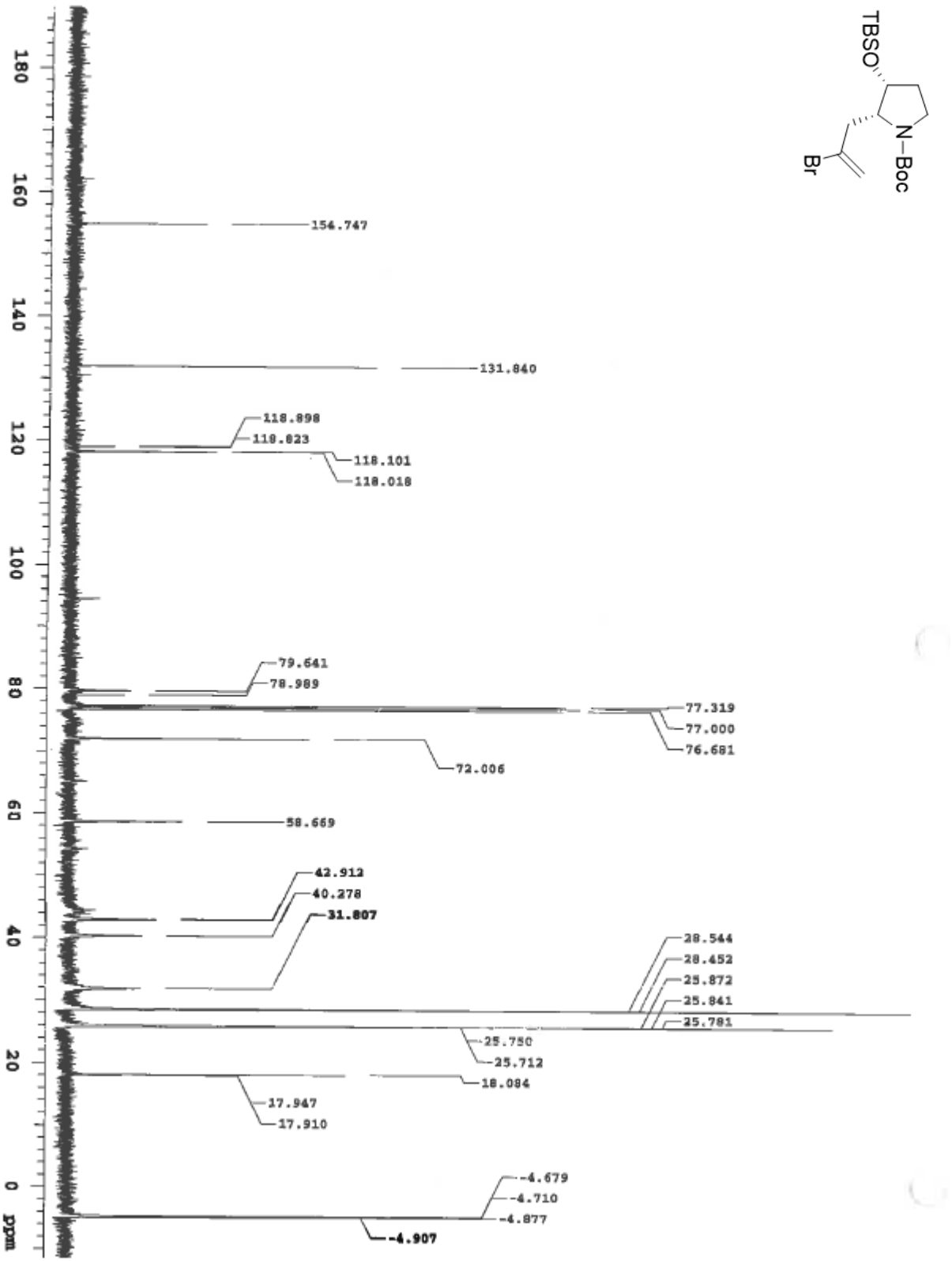

Figure 46: ^{13}C NMR (65 ℃) of 2-(2-bromo-allyl)-3-(*t*-butyl-dimethyl-silanyloxy)-pyrrolidine-1-carboxylic acid *t*-butyl ester **(29)**

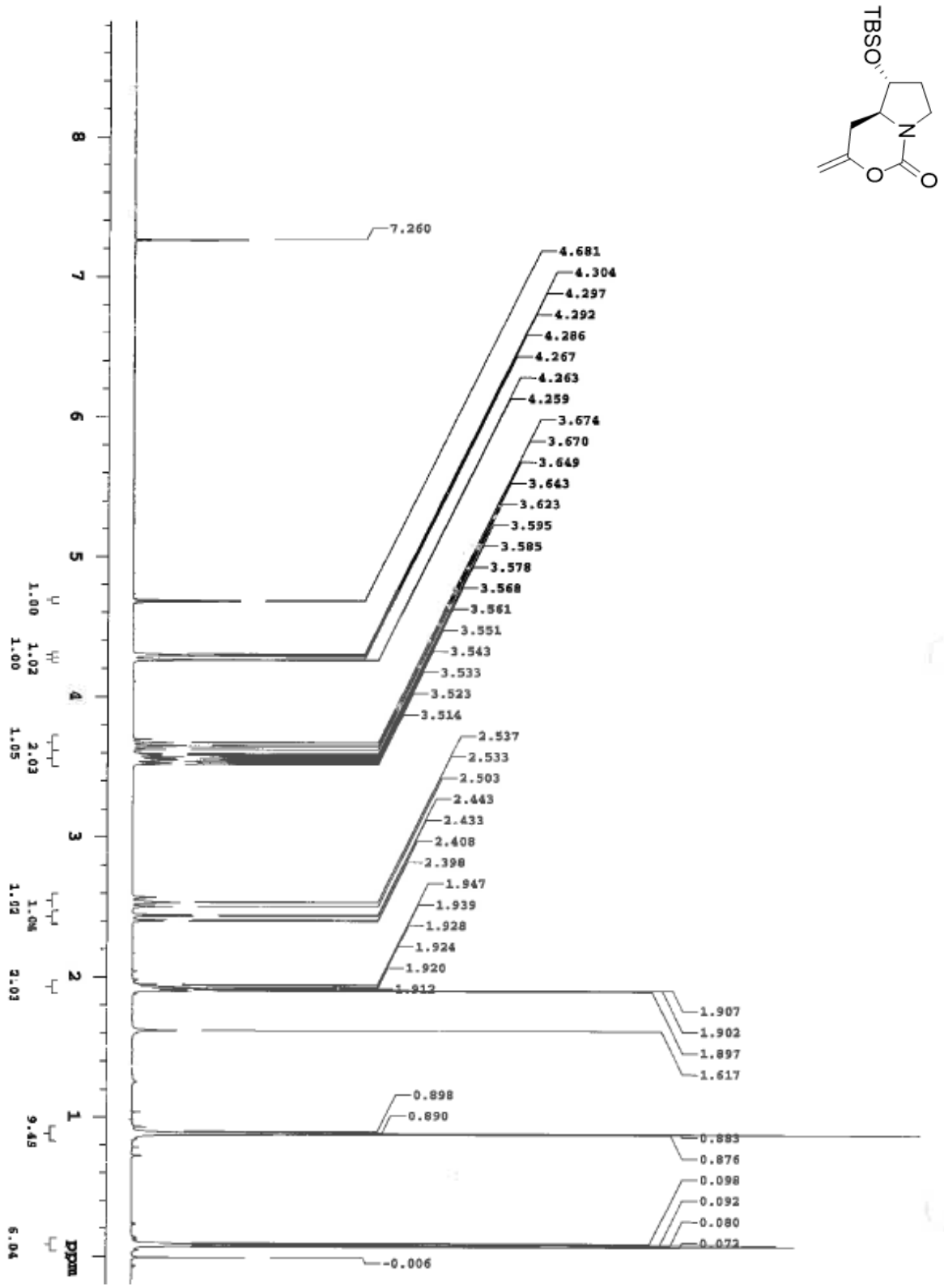

Figure 47: ^{1}H NMR of 5-(*t*-butyl-dimethyl-silanyloxy)-3-methylene-hexahydro-pyrrolo[1,2-c][1,3]oxazin-1-one **(30)**

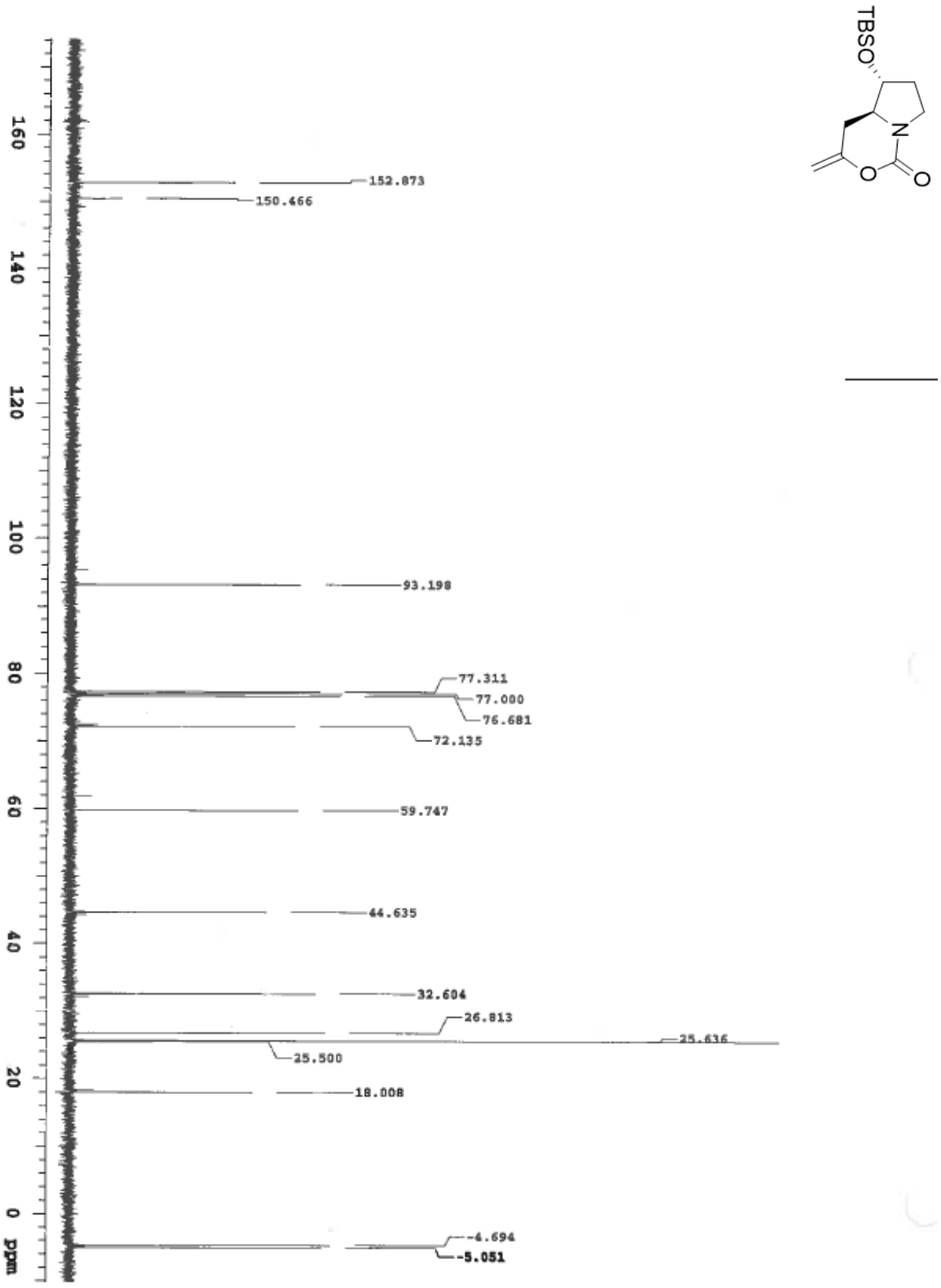

Figure 48: ^{13}C NMR of 5-(*t*-butyl-dimethyl-silanyloxy)-3-methylene-hexahydro-pyrrolo[1,2-c][1,3]oxazin-1-one **(30)**

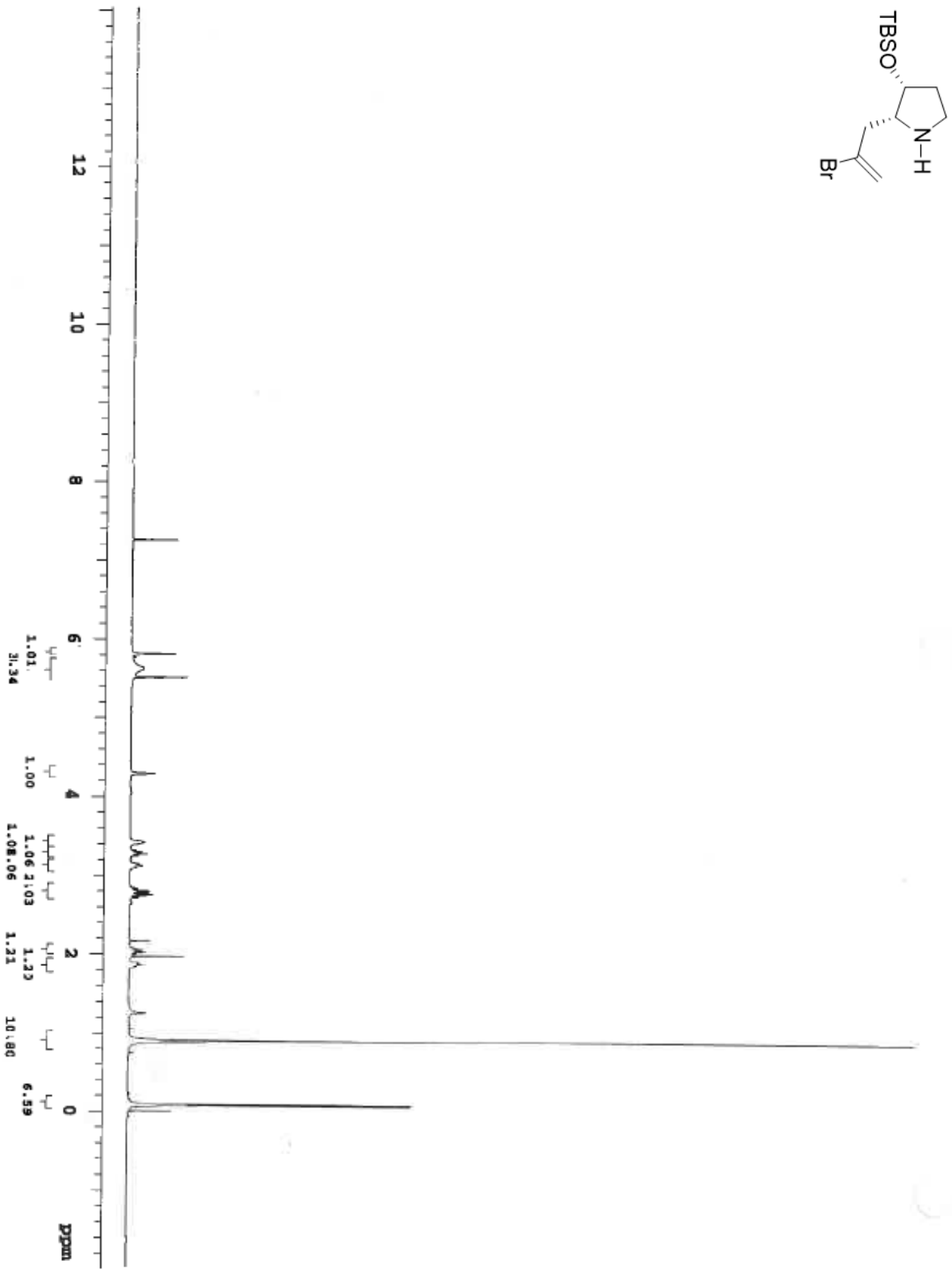

Figure 49: ^{1}H NMR of 2-(2-bromo-allyl)-3-(*t*-butyl-dimethyl-silanyloxy)-pyrrolidine **(31)**

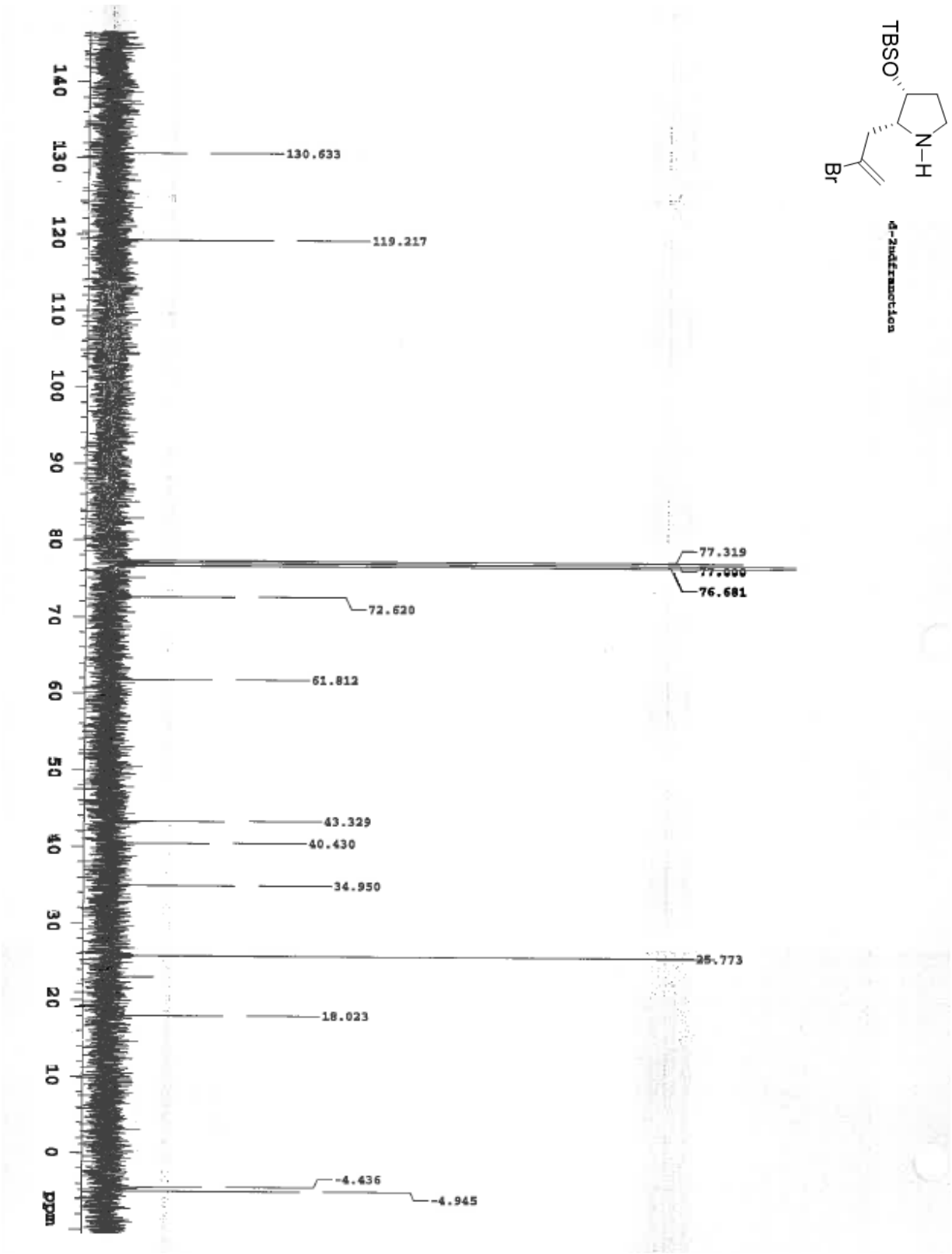

Figure 50: ^{13}C NMR of 2-(2-bromo-allyl)-3-(*t*-butyl-dimethyl-silanyloxy)-pyrrolidine **(31)**

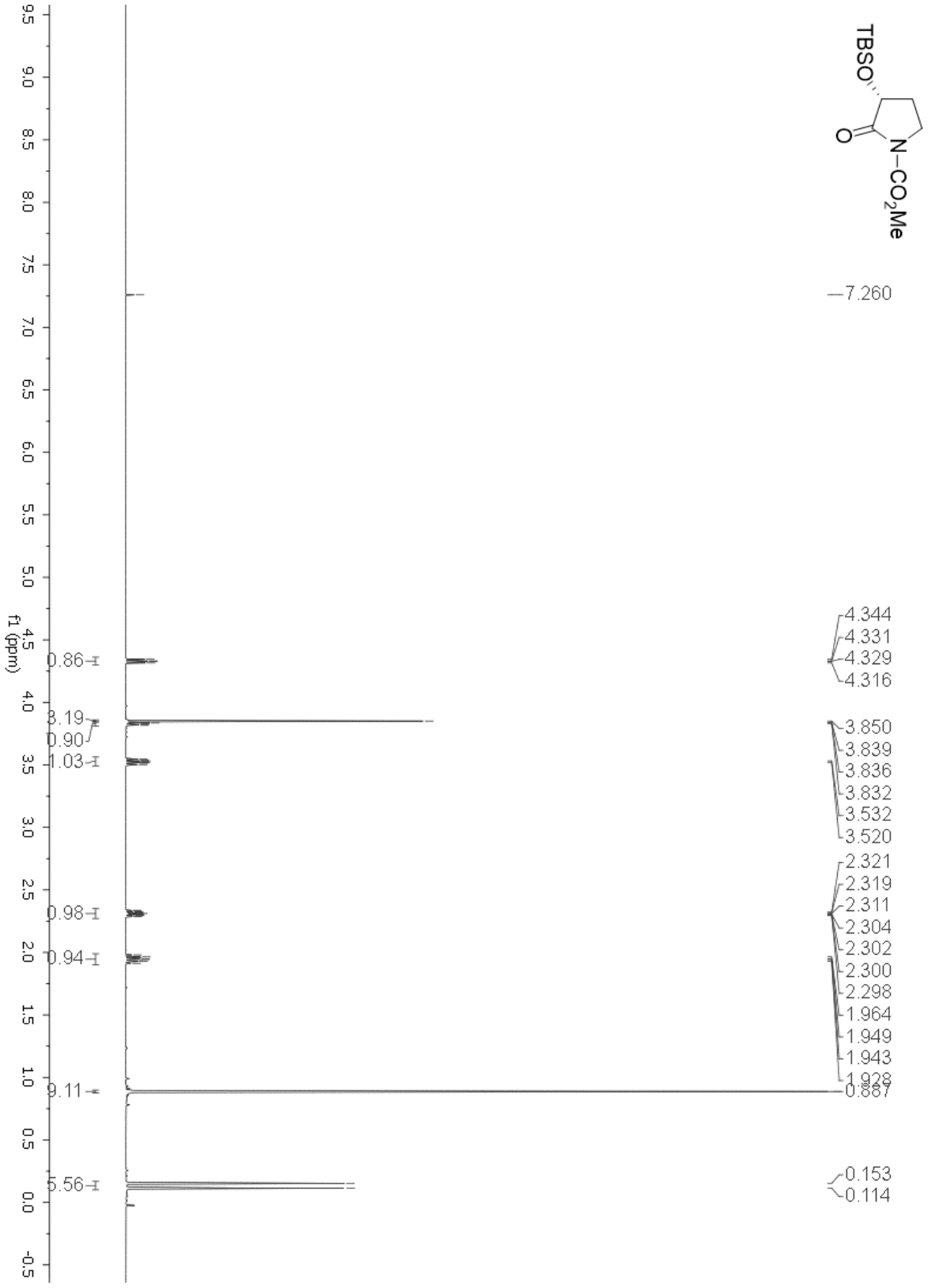

Figure 51: ^{1}H NMR of 3(R)-*t*-butyldimethylsilyloxy-1-(methoxycarbonyl)pyrrolidin-2-one **(33)**

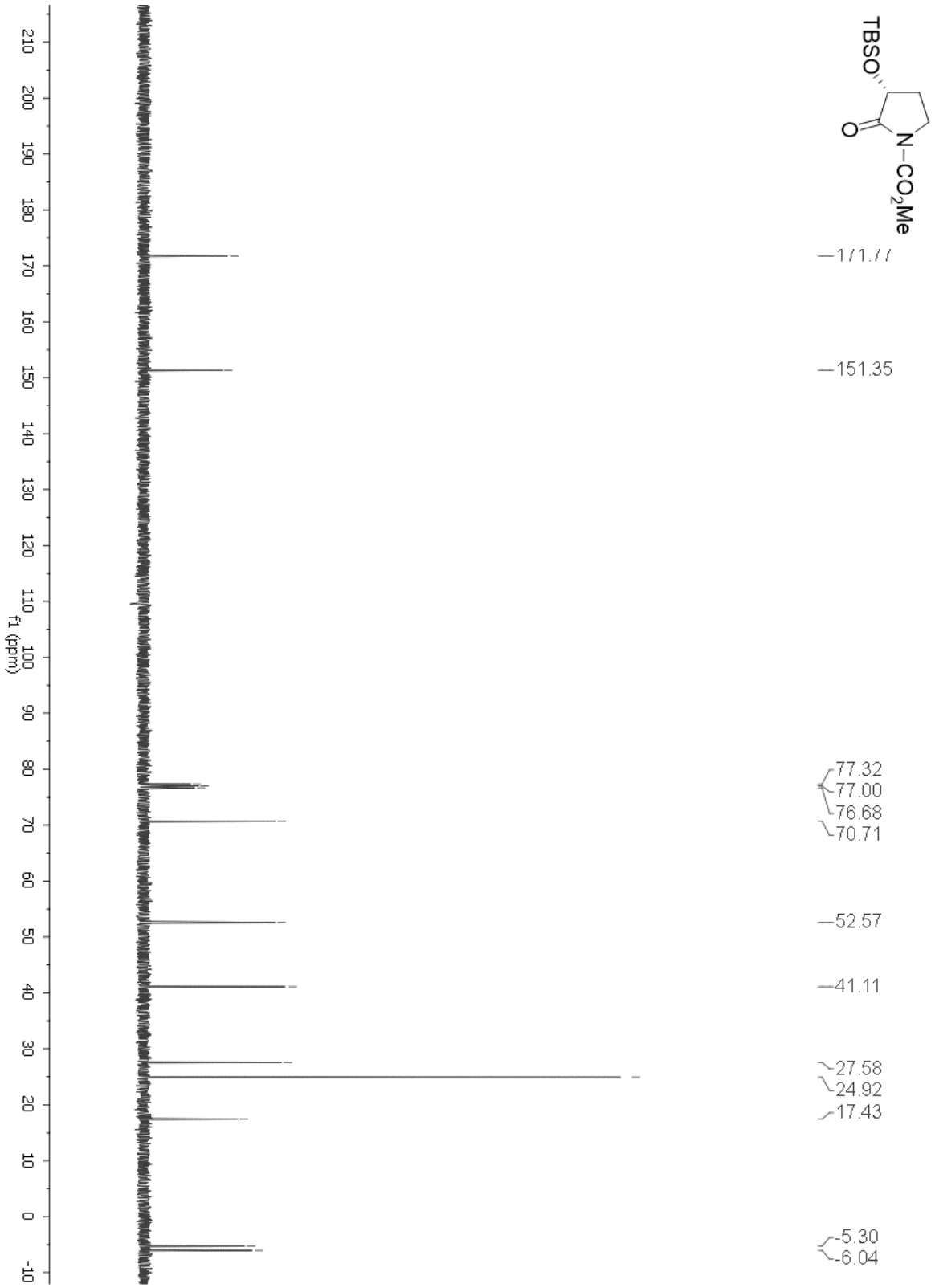

Figure 52: ^{13}C NMR of 3(R)-*t*-butyldimethylsilyloxy-1-(methoxycarbonyl)pyrrolidin-2-one **(33)**

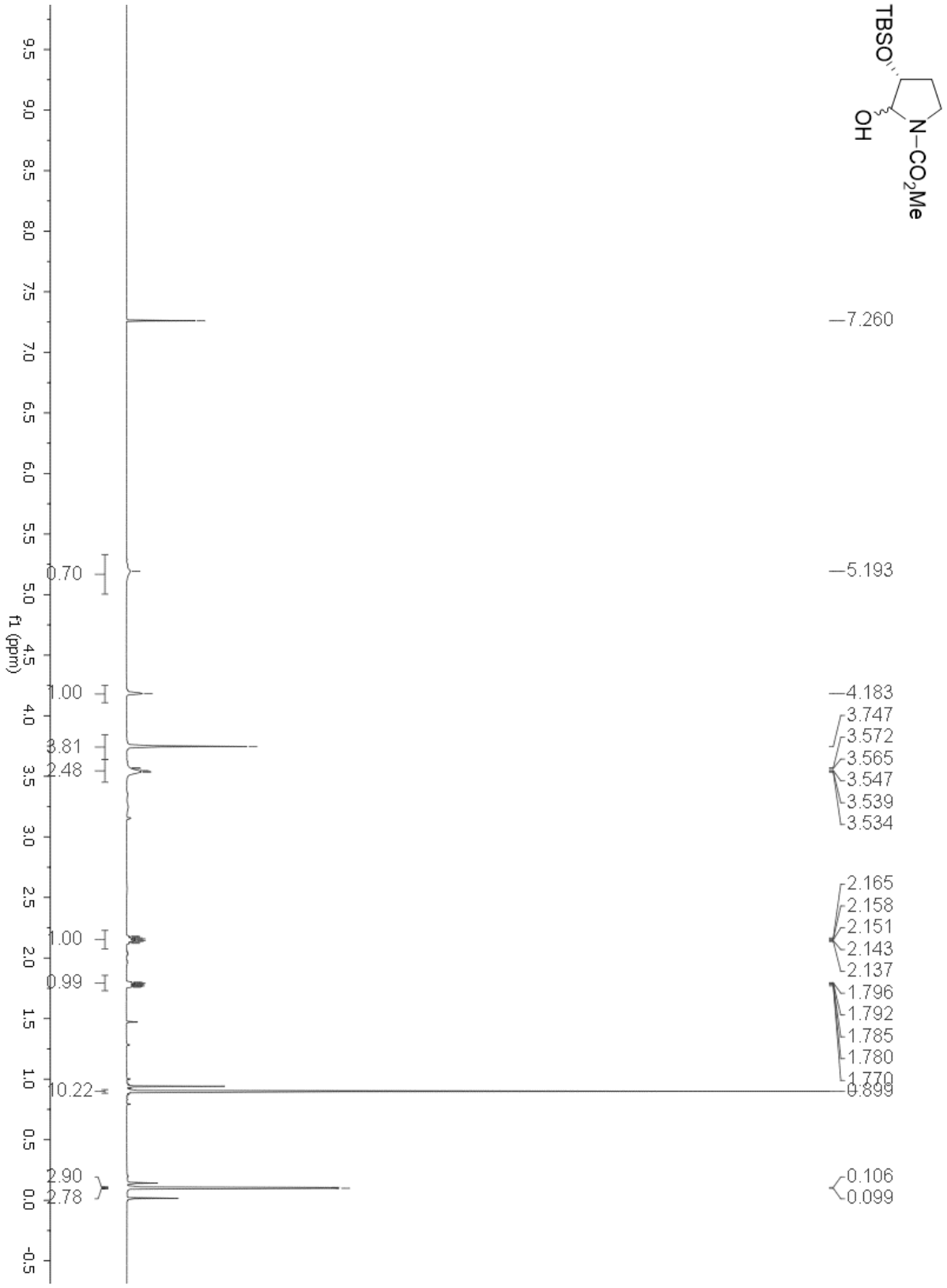

Figure 53: ^{1}H NMR (65 ℃) of 3(R)-*t*-butyldimethylsilyloxy-2(R/S)-hydroxy-1-(methoxycarbonyl)pyrrolidine **(34)**

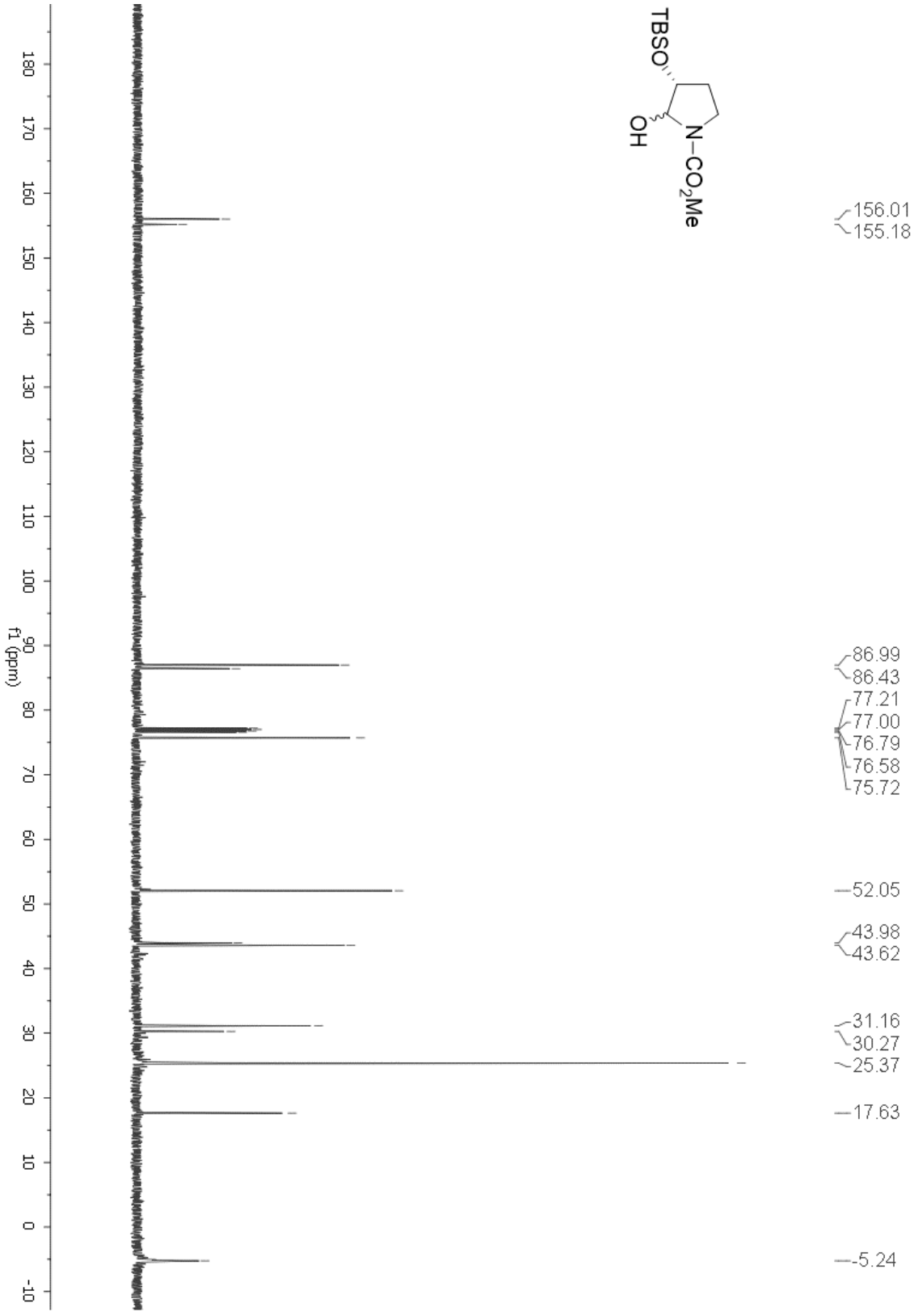

Figure 54: ^{13}C NMR of 3(R)-*t*-butyldimethylsilyloxy-2(R/S)-hydroxy-1-(methoxycarbonyl)pyrrolidine **(34)**

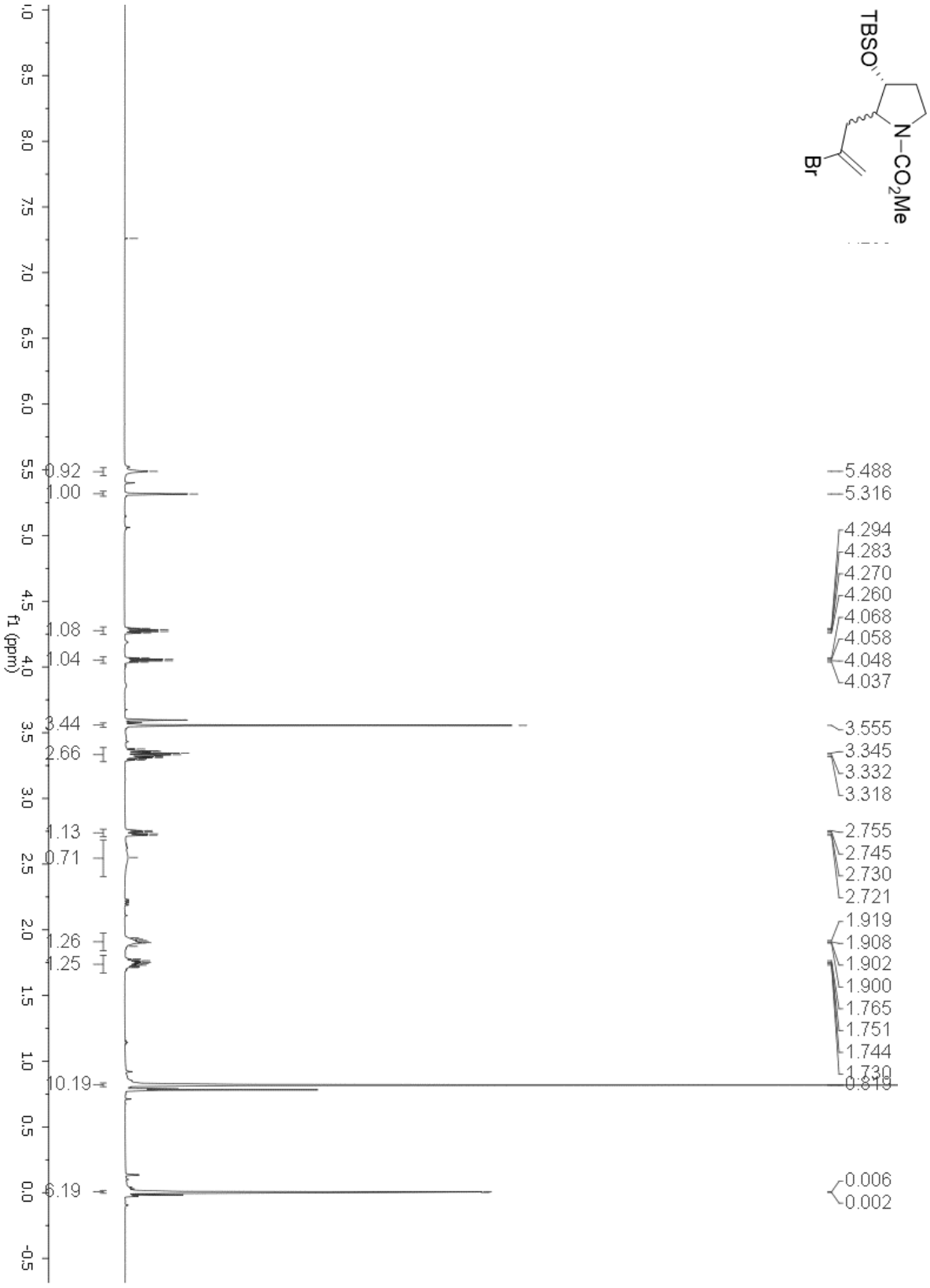

Figure 55: ^{1}H NMR (65 ℃) of 2(R/S)-(2-bromo-2-propen-1-yl)-3(R)-*t*-butyldimethyl-silyloxy-1-(methoxycarbonyl)pyrrolidine **(32)**

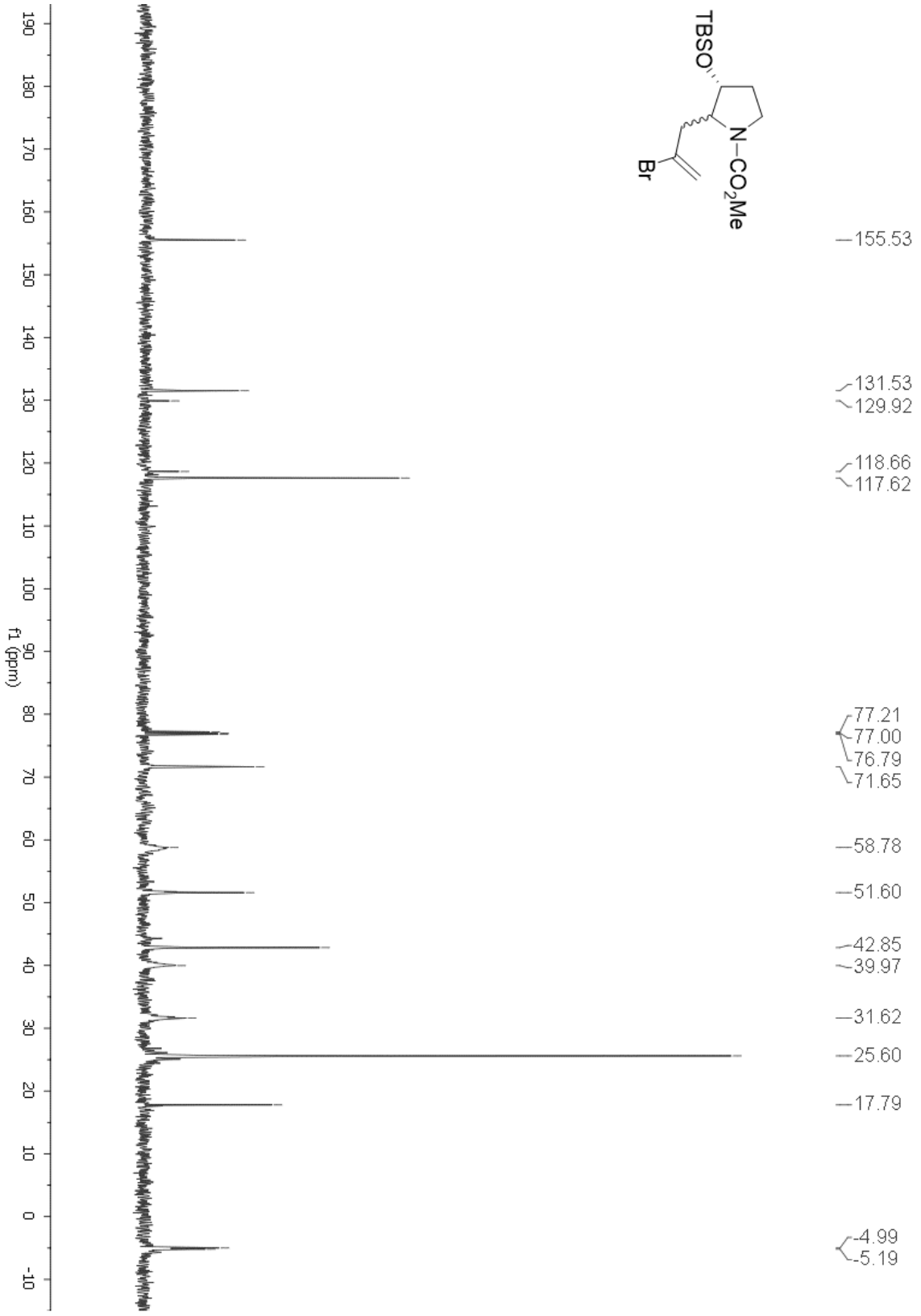

Figure 56: ^{13}C NMR (65 ℃) of 2(R/S)-(2-bromo-2-propen-1-yl)-3(R)-*t*-butyldimethyl-silyloxy-1-(methoxycarbonyl)pyrrolidine **(32)**

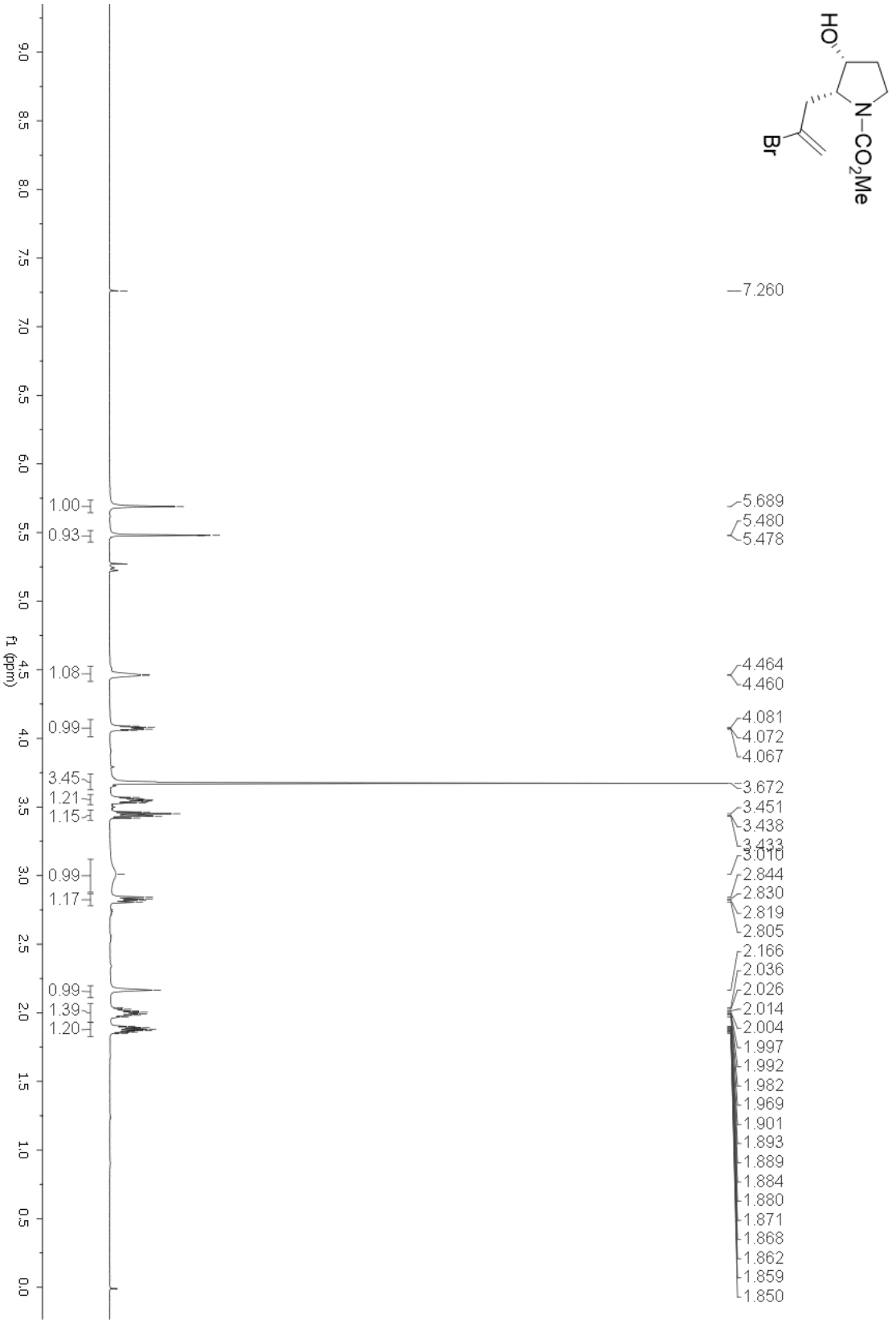

Figure 57: ^{1}H NMR (65 ℃) of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)pyrrolidine **(35)**

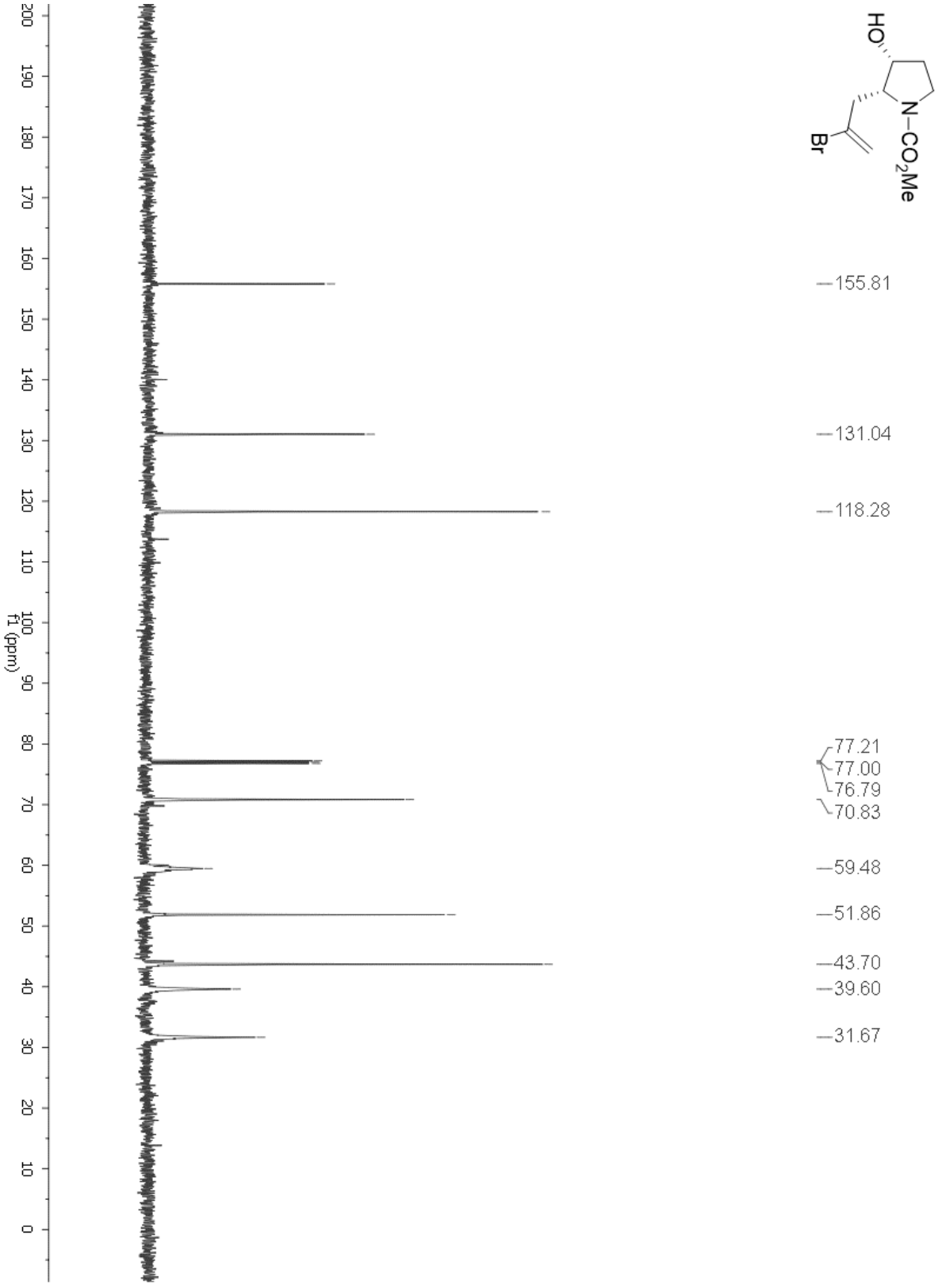

Figure 58: ^{13}C NMR (65 ℃) of 2(R)-(2-bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)-pyrrolidine **(35)**

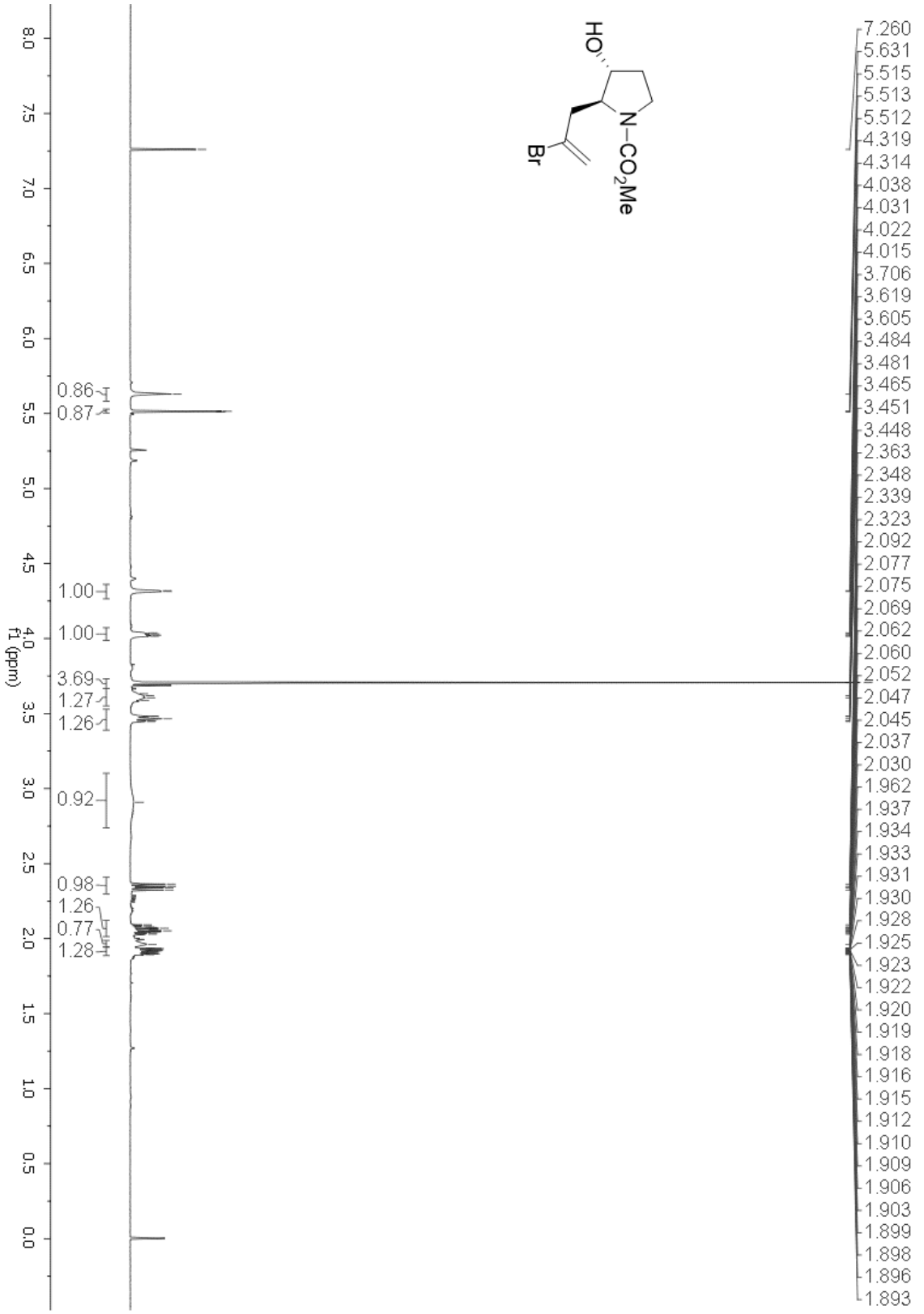

Figure 59: ^{1}H NMR (60 ℃) of 2(S)-(2-bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)pyrrolidine **(36)**

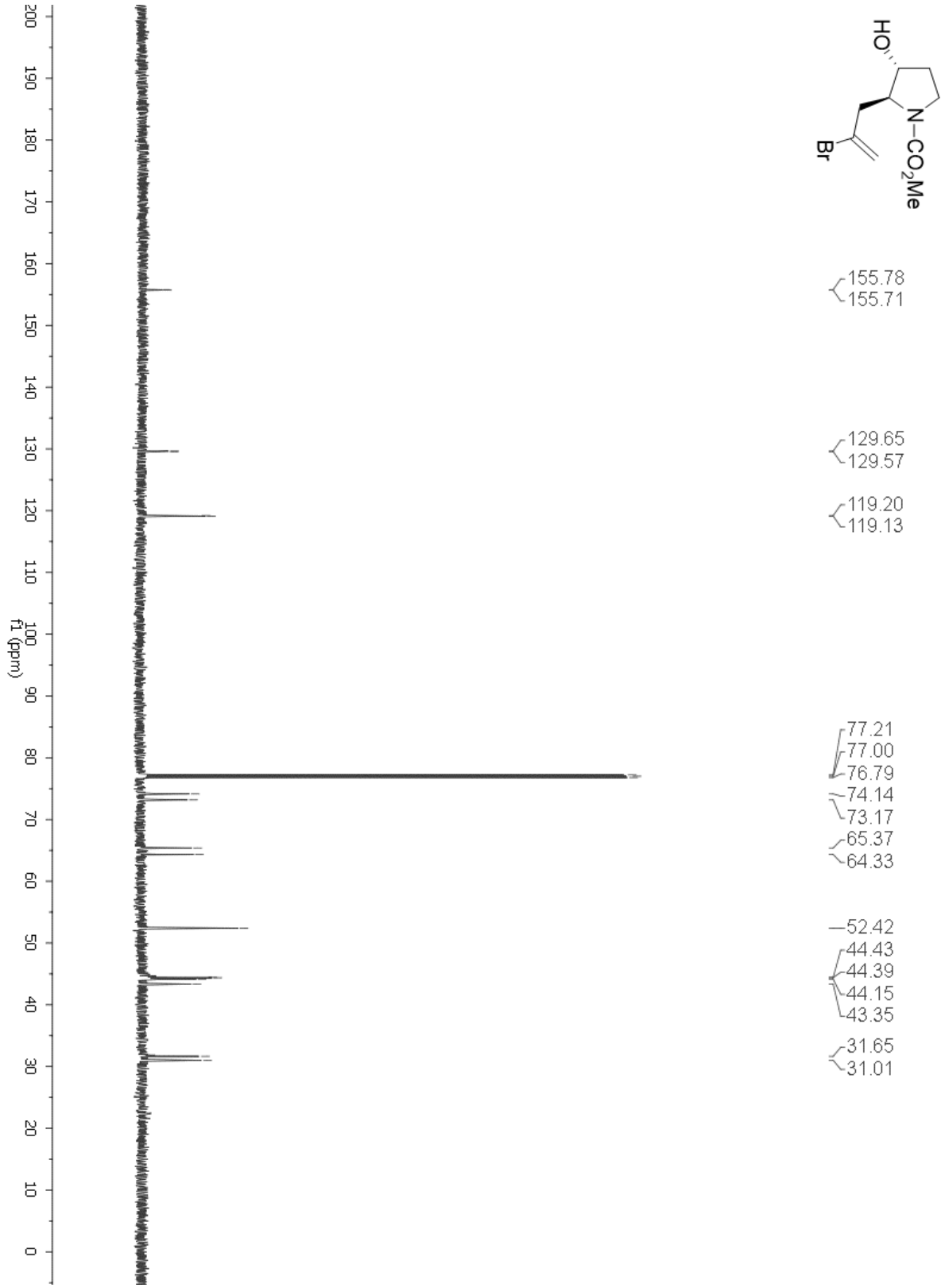

Figure 60: ^{13}C NMR of 2(S)-(2-bromo-2-propen-1-yl)-3(R)-hydroxy-1-(methoxycarbonyl)-pyrrolidine **(36)**

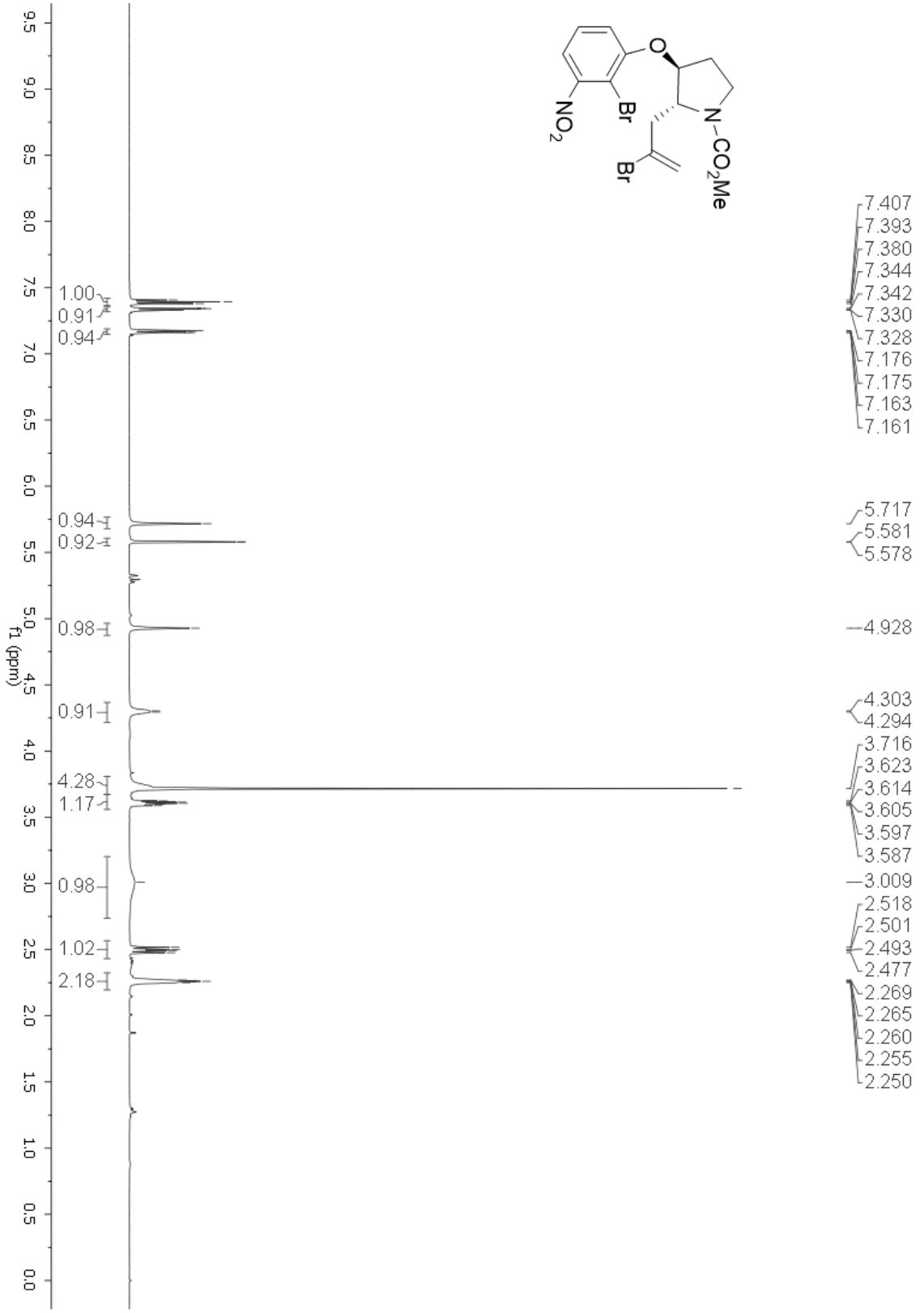

Figure 61: ^{1}H NMR (65 ℃) of 3(S)-(2-bromo-3-nitrophenyl)-2(R)-(2-bromo-2-propen-1-yl)-1-(methoxycarbonyl)pyrrolidine **(37)**

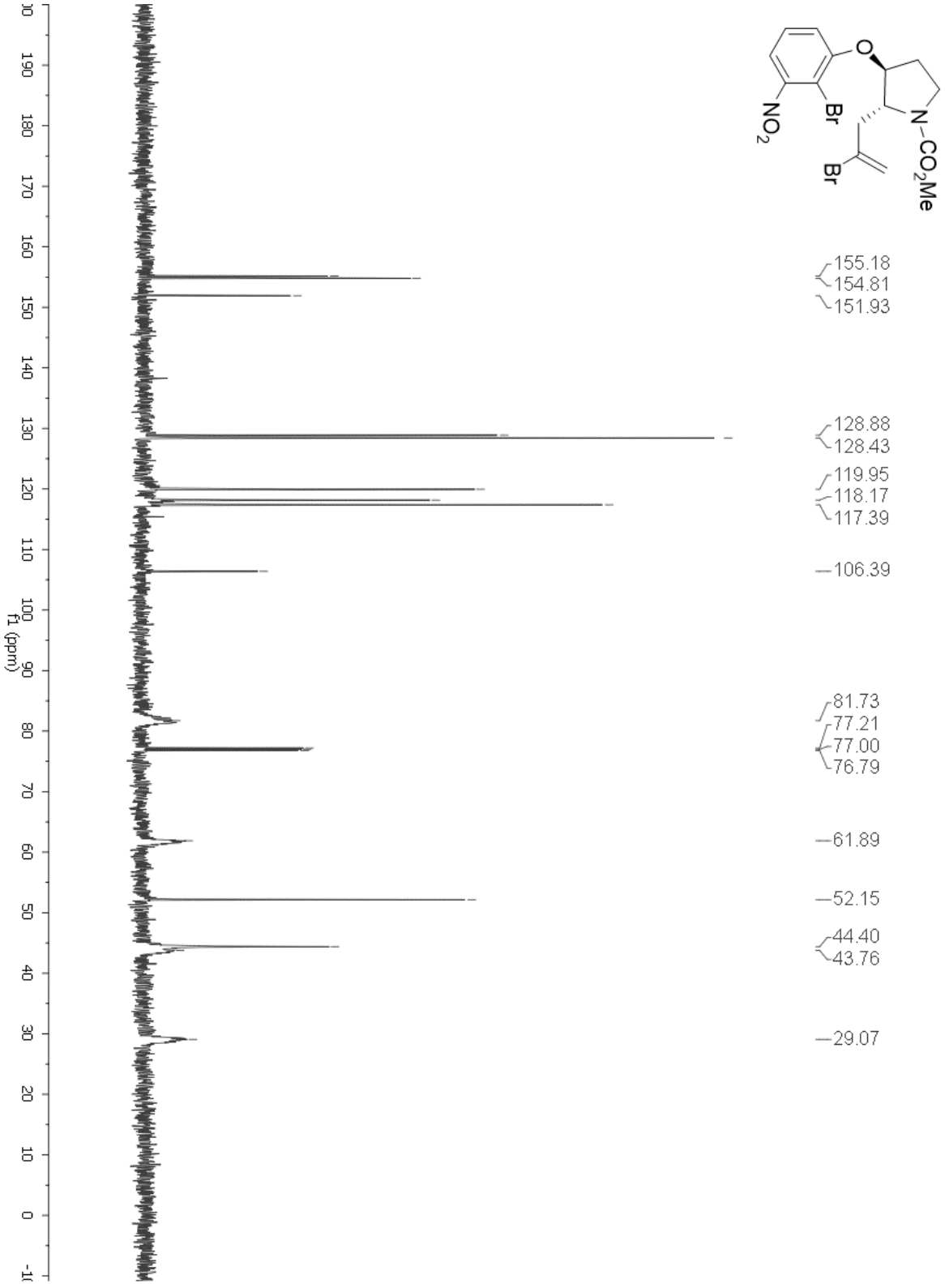

Figure 62: ^{13}C NMR (65 ℃) of 3(S)-(2-bromo-3-nitrophenyl)-2(R)-(2-bromo-2-propen-1-yl)-1-(methoxycarbonyl)pyrrolidine **(37)**

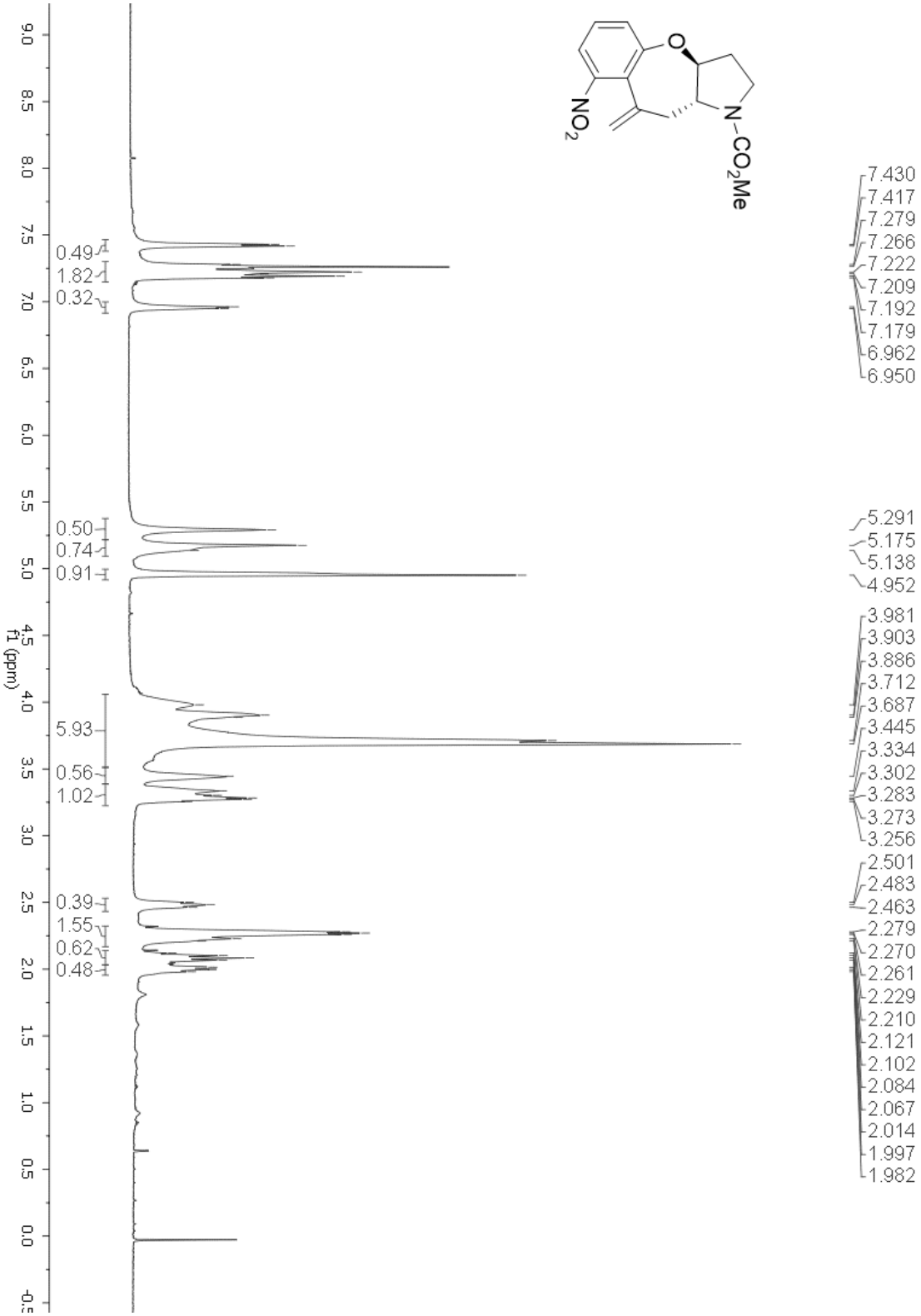

Figure 63: ^{1}H NMR of 2,3,3a(S),9,10,10a(R)-hexahydro-1-(methoxycarbonyl)-8-nitro-1H-benzoxepino[3,2-b]pyrrole **(38)**

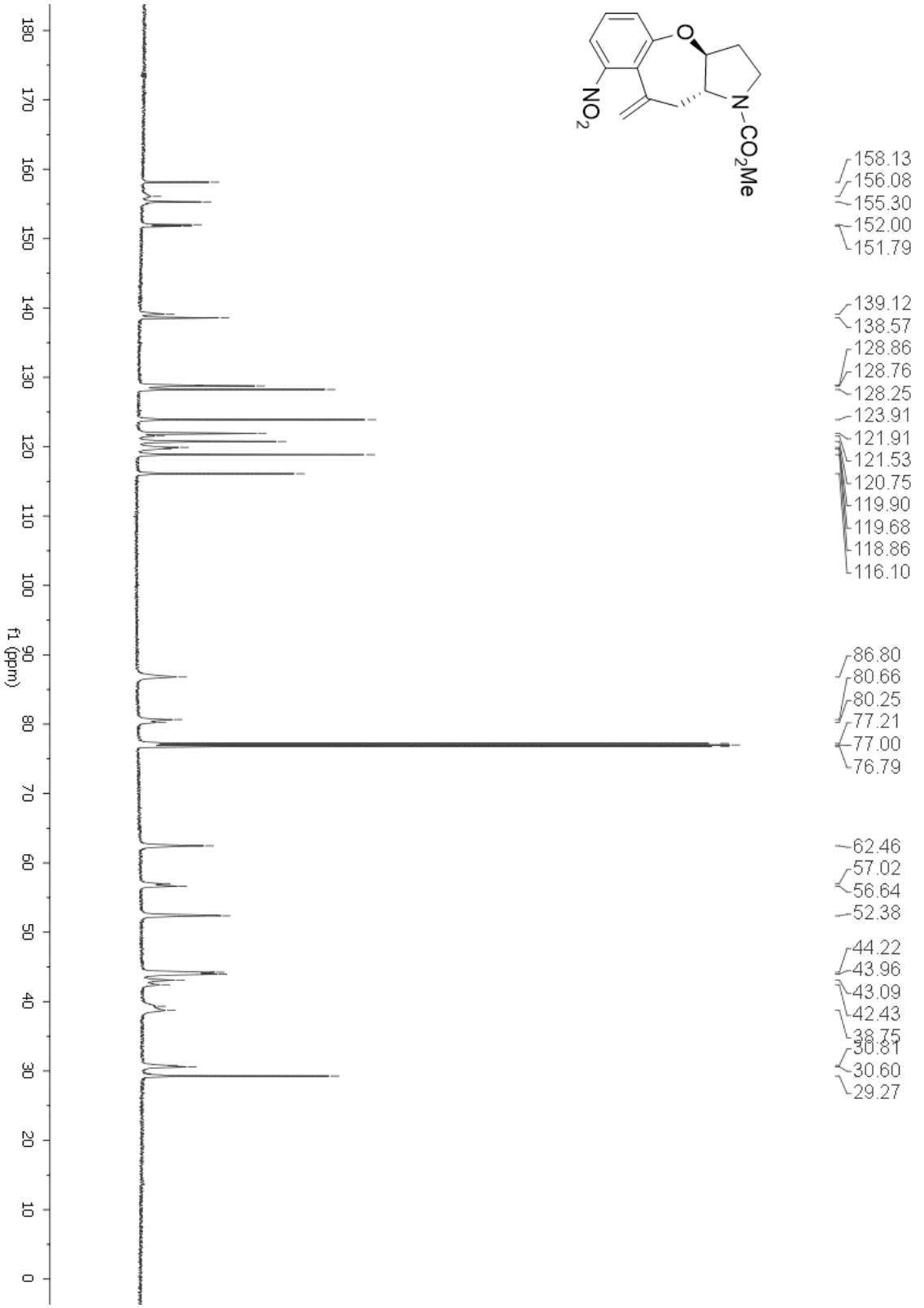

Figure 64: ^{13}C NMR of 2,3,3a(S),9,10,10a(R)-hexahydro-1-(methoxycarbonyl)-8-nitro-1H-benzoxepino[3,2-b]pyrrole **(38)**

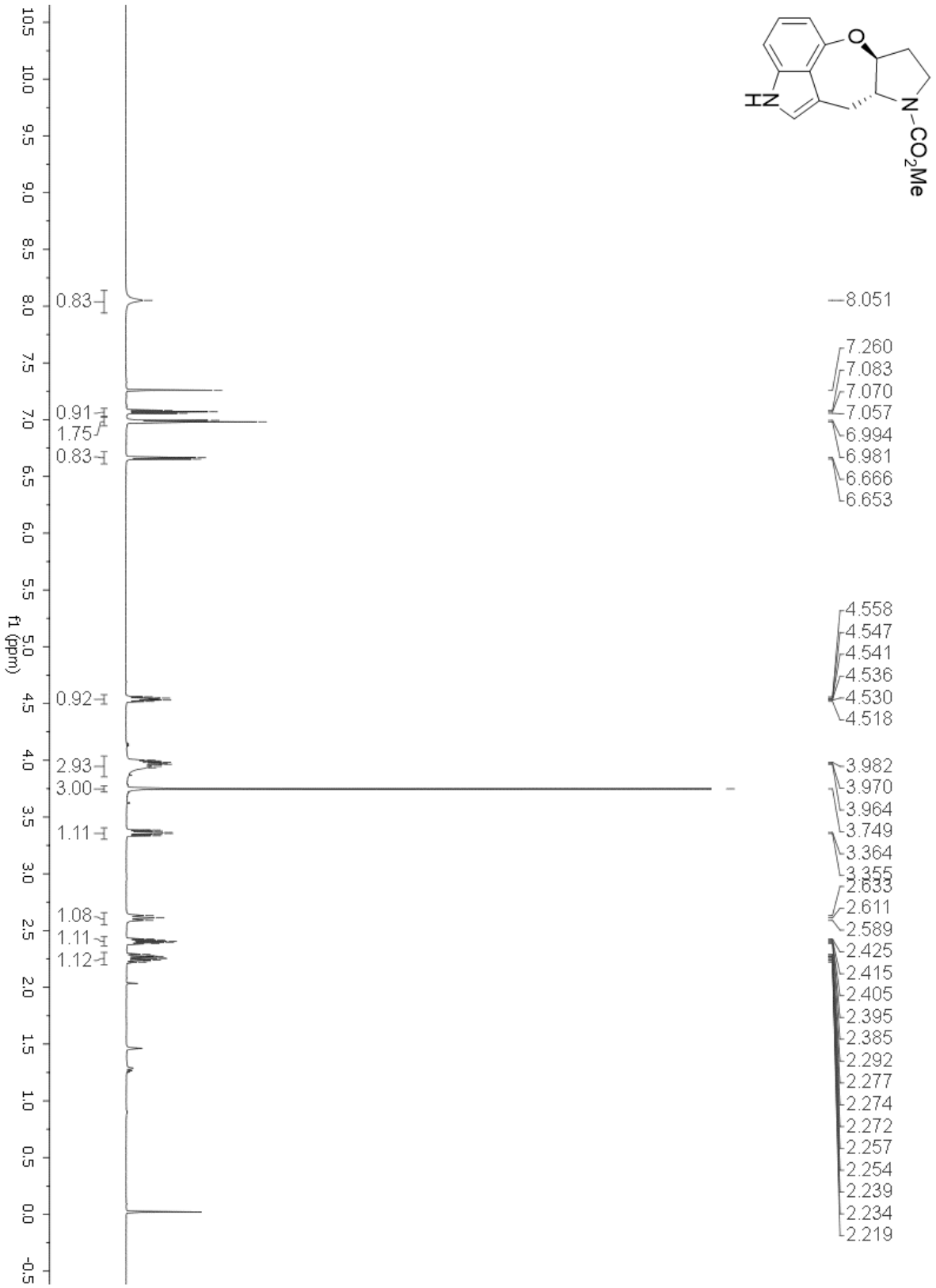

Figure 65: ^{1}H NMR (65 ℃) of 6,6a(*R*),7,8,9,9a(*S*)-hexahydro-7-(methoxycarbonyl)-4*H*-pyrrolo[2',3':6,7]oxepino-[4,3,2-*cd*]indole **(39)**

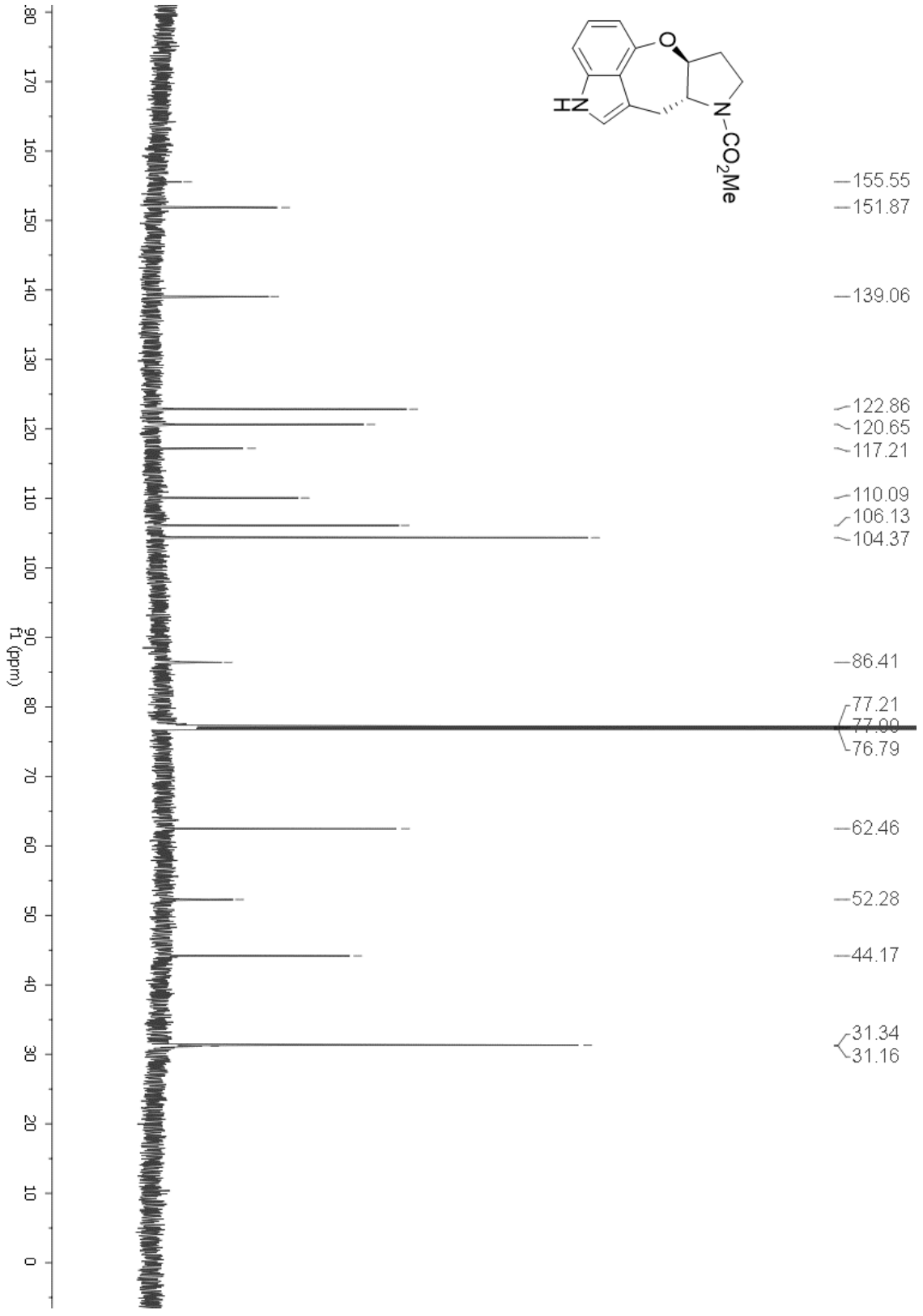

Figure 66: ^{13}C NMR (65 ℃) of 6,6a(*R*),7,8,9,9a(*S*)-hexahydro-7-(methoxycarbonyl)-4*H*-pyrrolo[2',3':6,7]oxepino-[4,3,2-*cd*]indole **(39)**

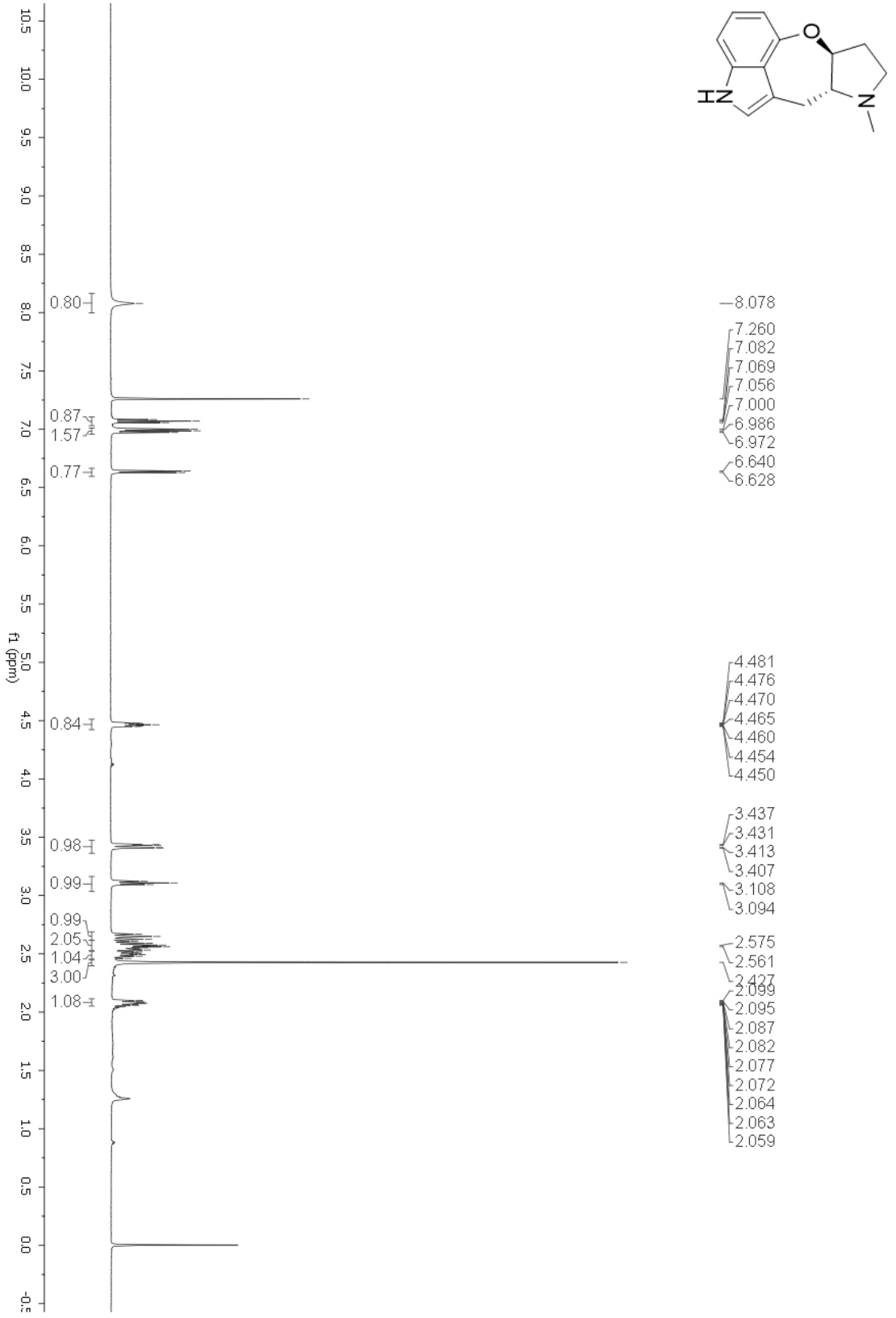

Figure 67: ^{1}H NMR of ht-13-A

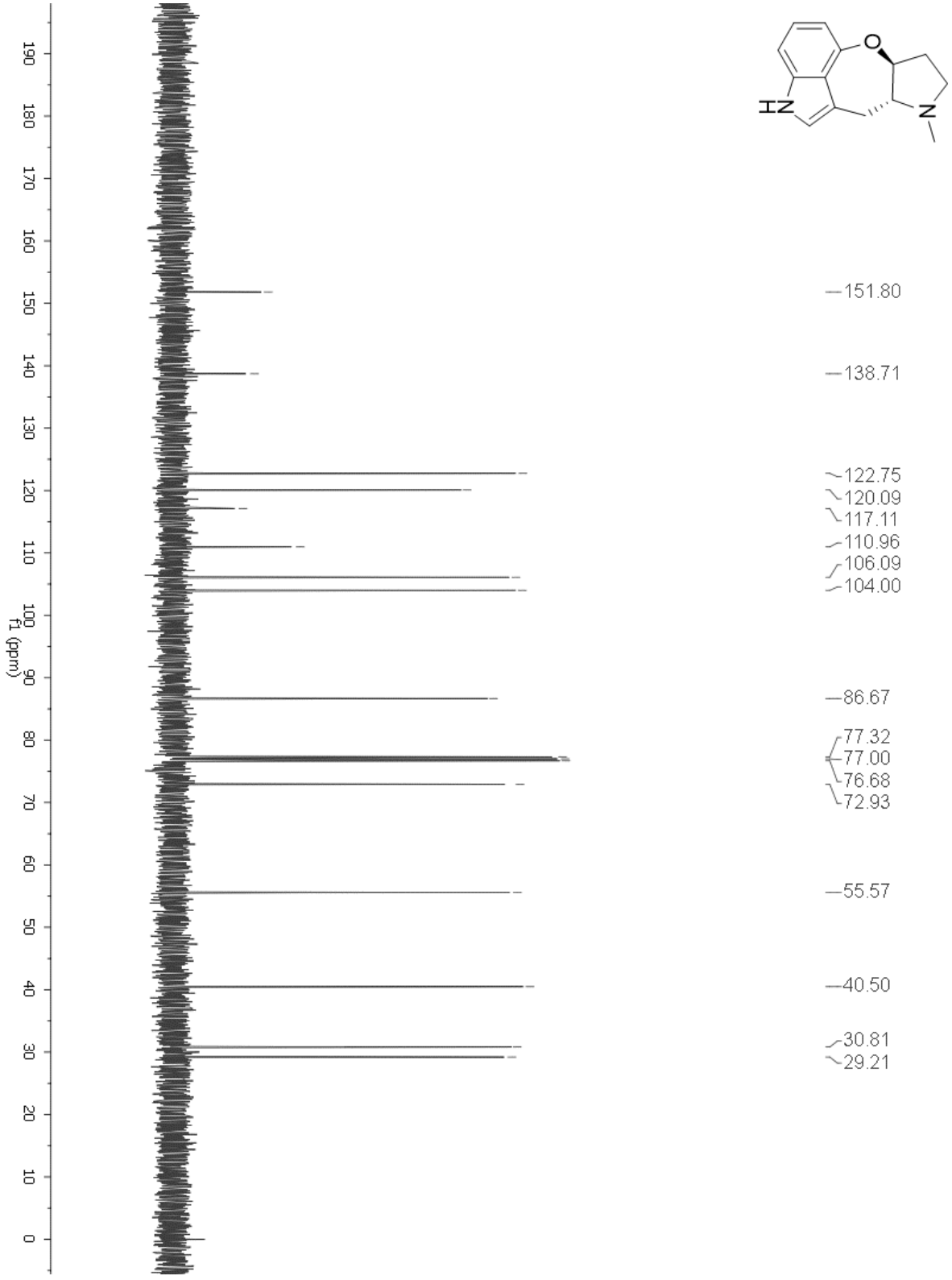

Figure 68: ^{13}C NMR of ht-13-A

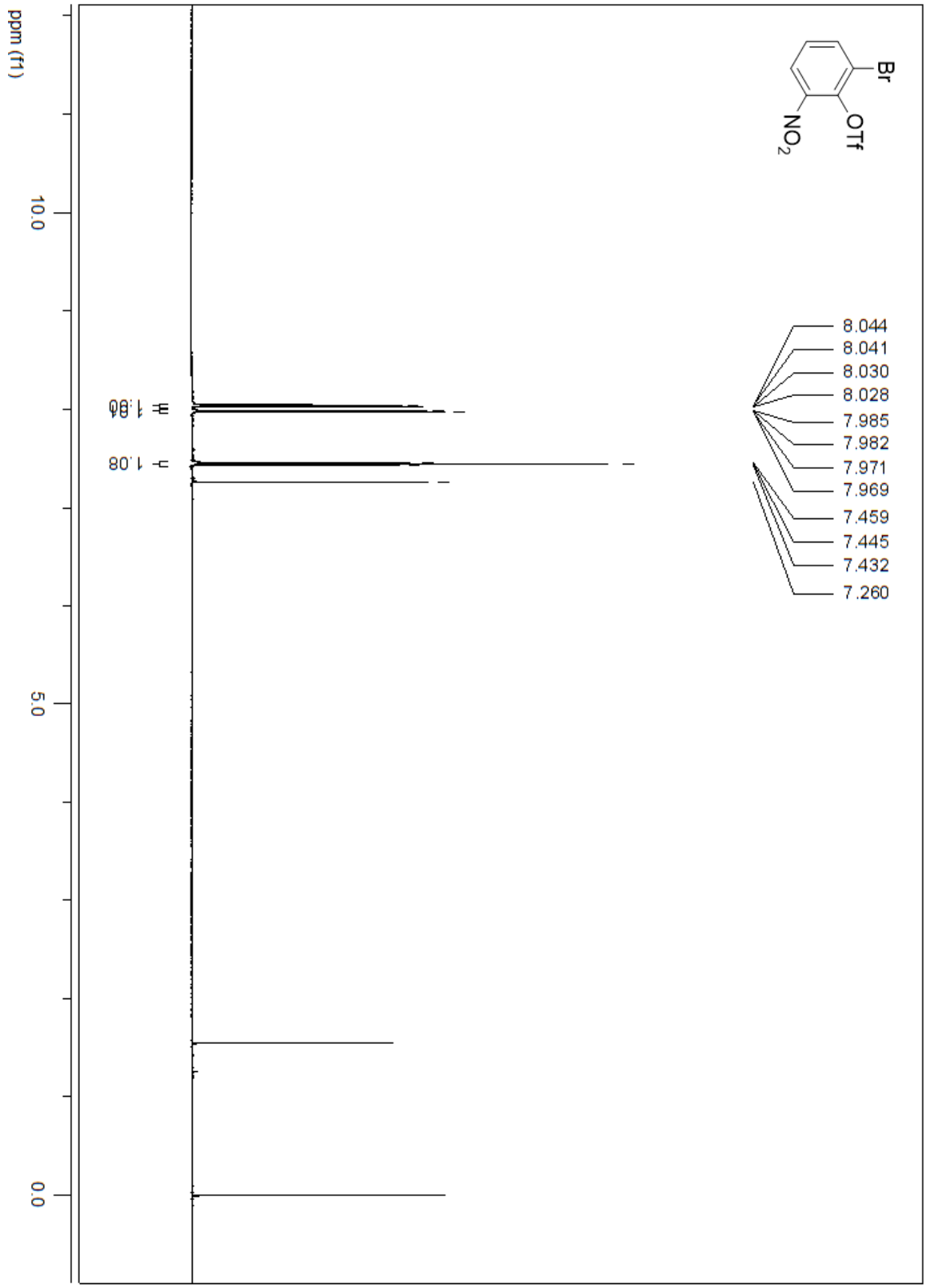

Figure 69: ^{1}H NMR of trifluoro-methanesulfonic acid 2-bromo-6-nitro-phenyl ester **(43)**

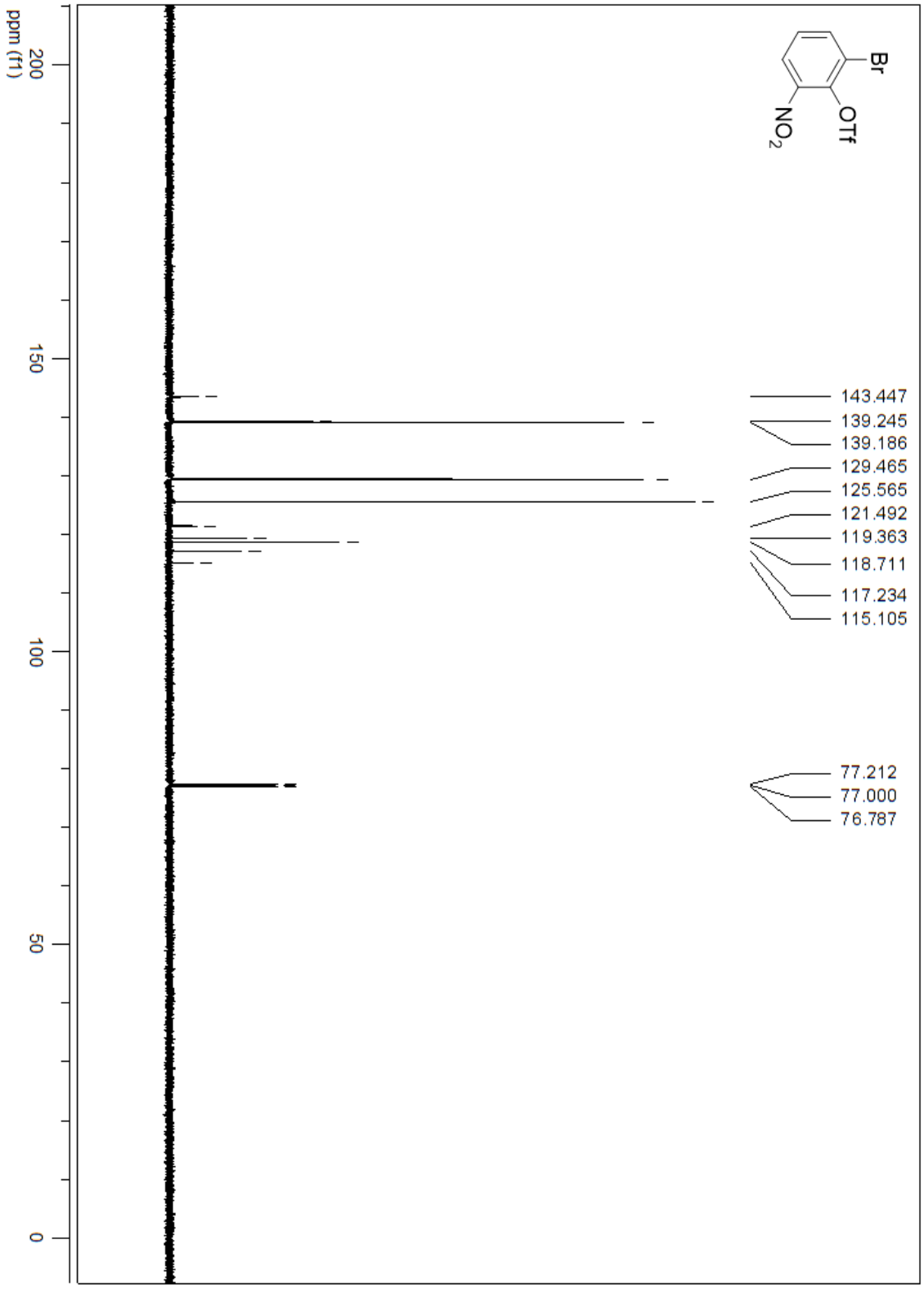

Figure 70: ^{13}C NMR of trifluoro-methanesulfonic acid 2-bromo-6-nitro-phenyl ester **(43)**

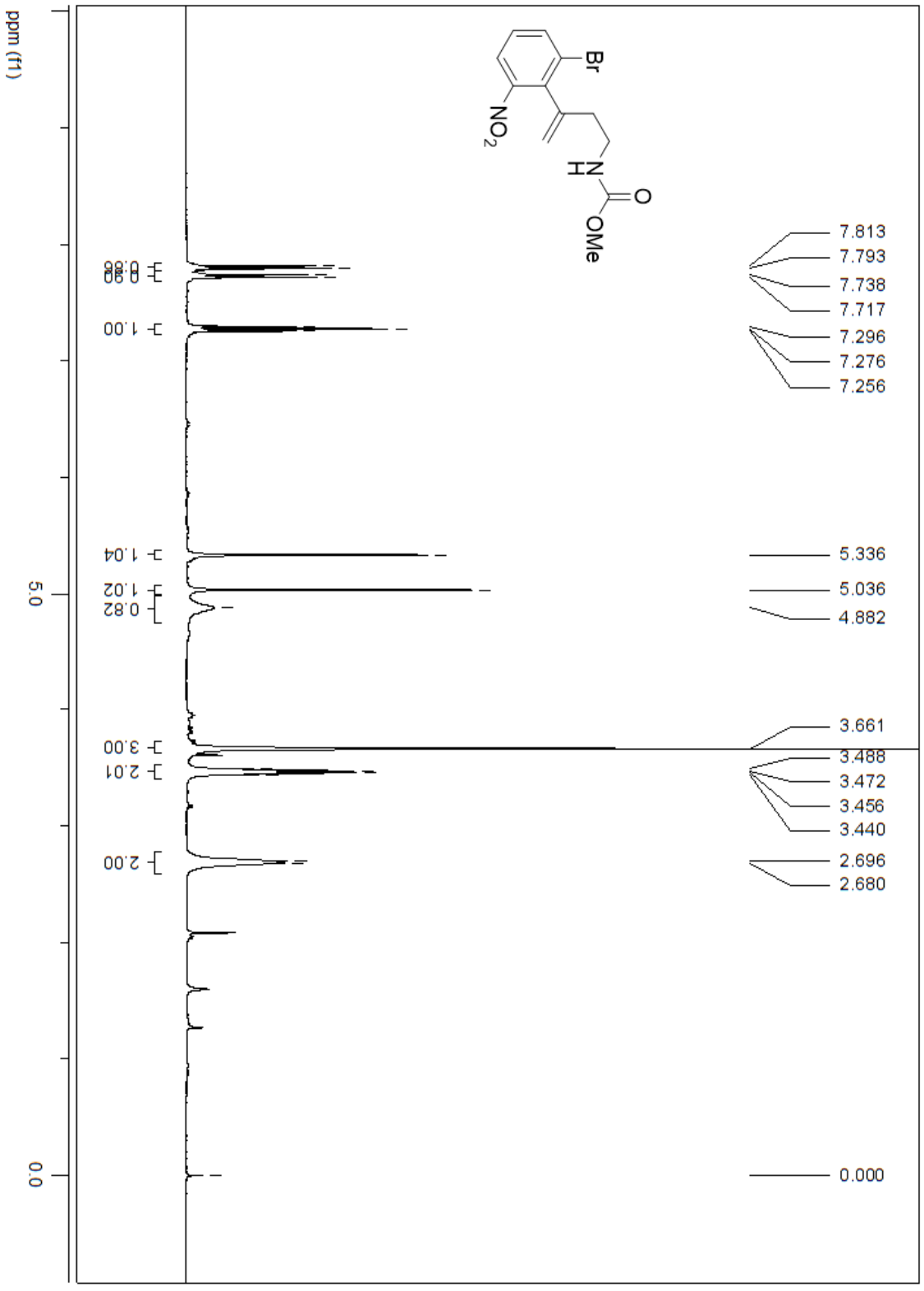

Figure 71: ^{1}H NMR (65 ℃) of [3-(2-bromo-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester **(45)**

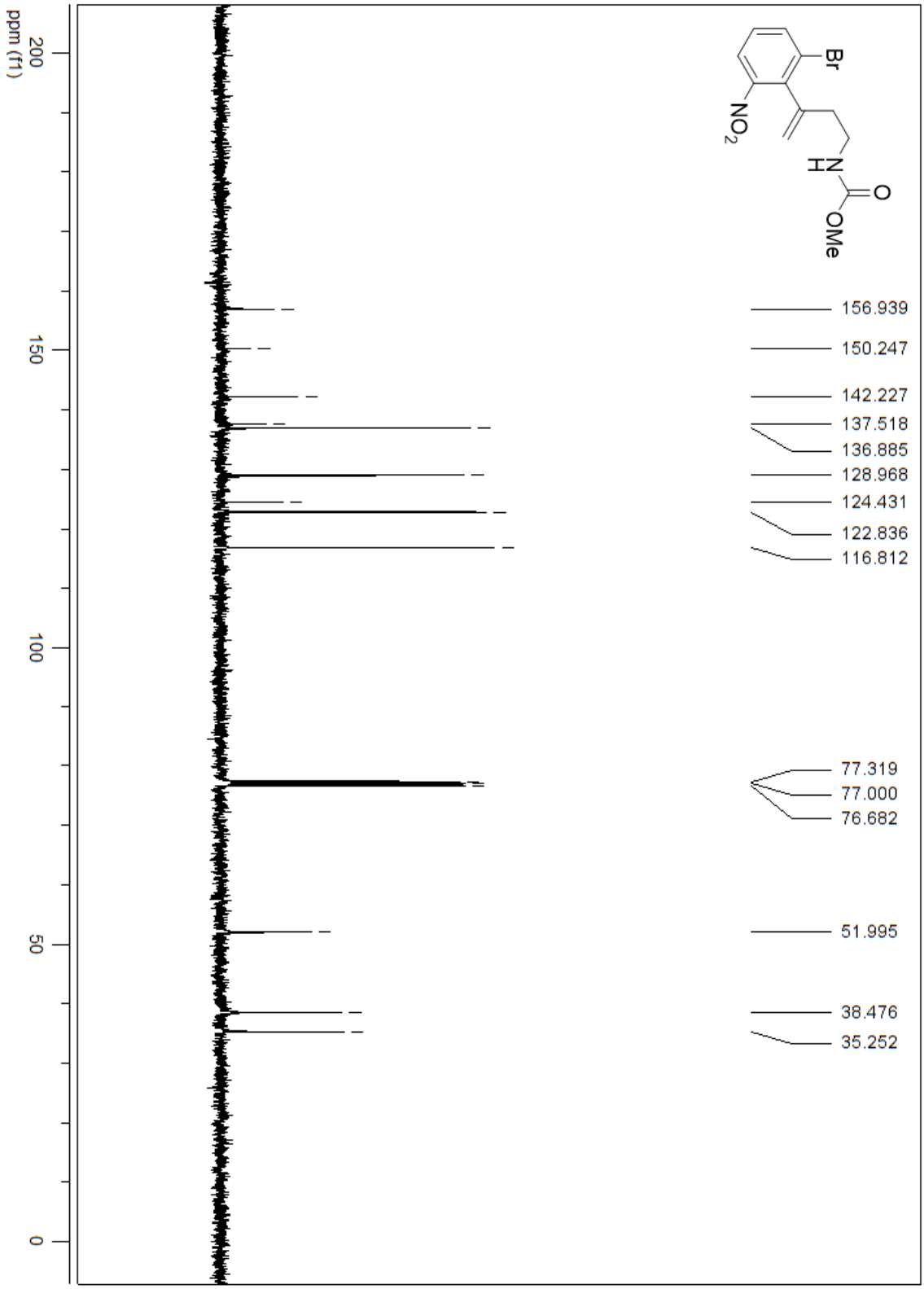

Figure 72: ^{13}C NMR of [3-(2-bromo-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester **(45)**

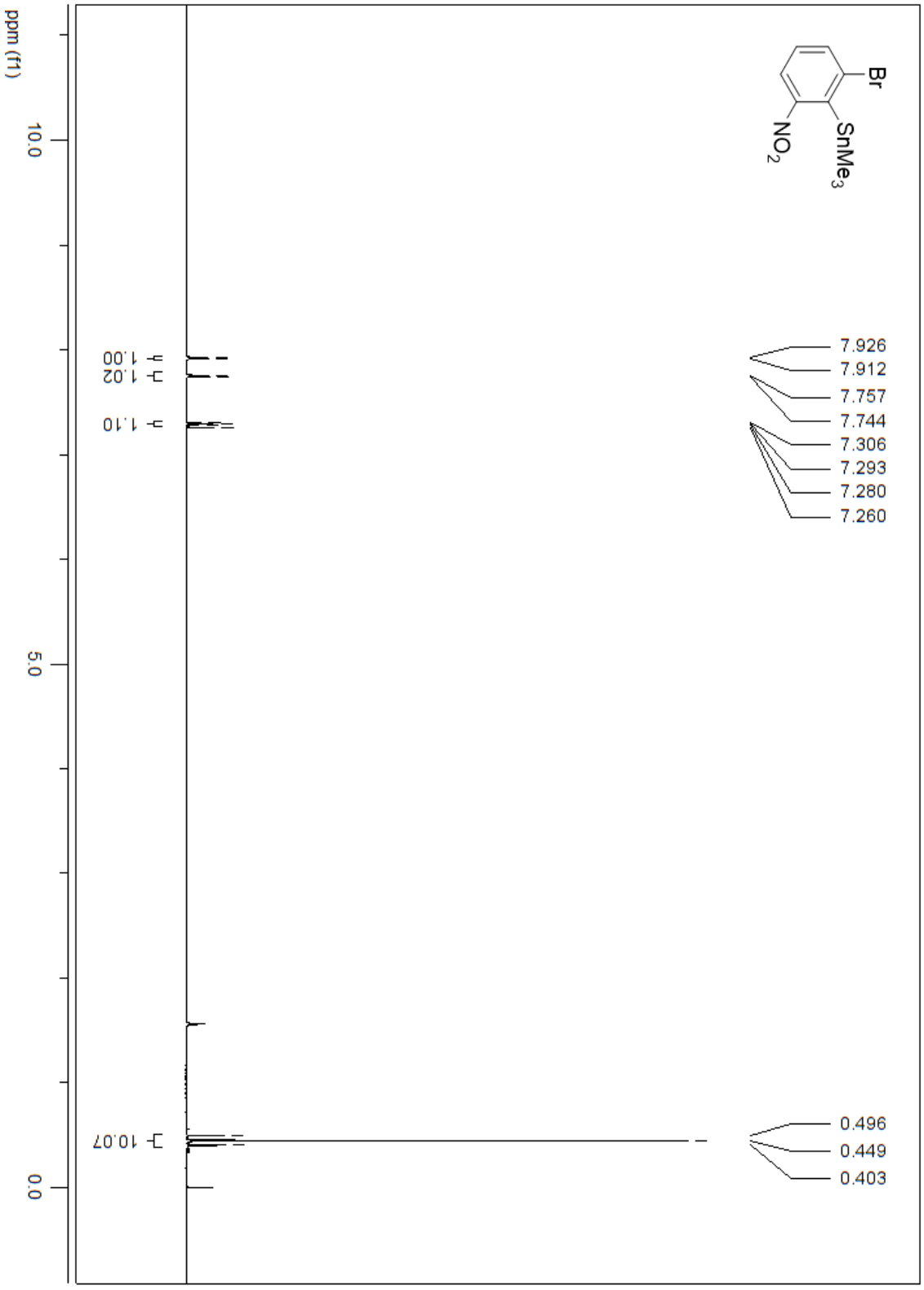

Figure 73: ^{1}H NMR of (2-bromo-6-nitro-phenyl)-trimethyl-stannane **(50)**

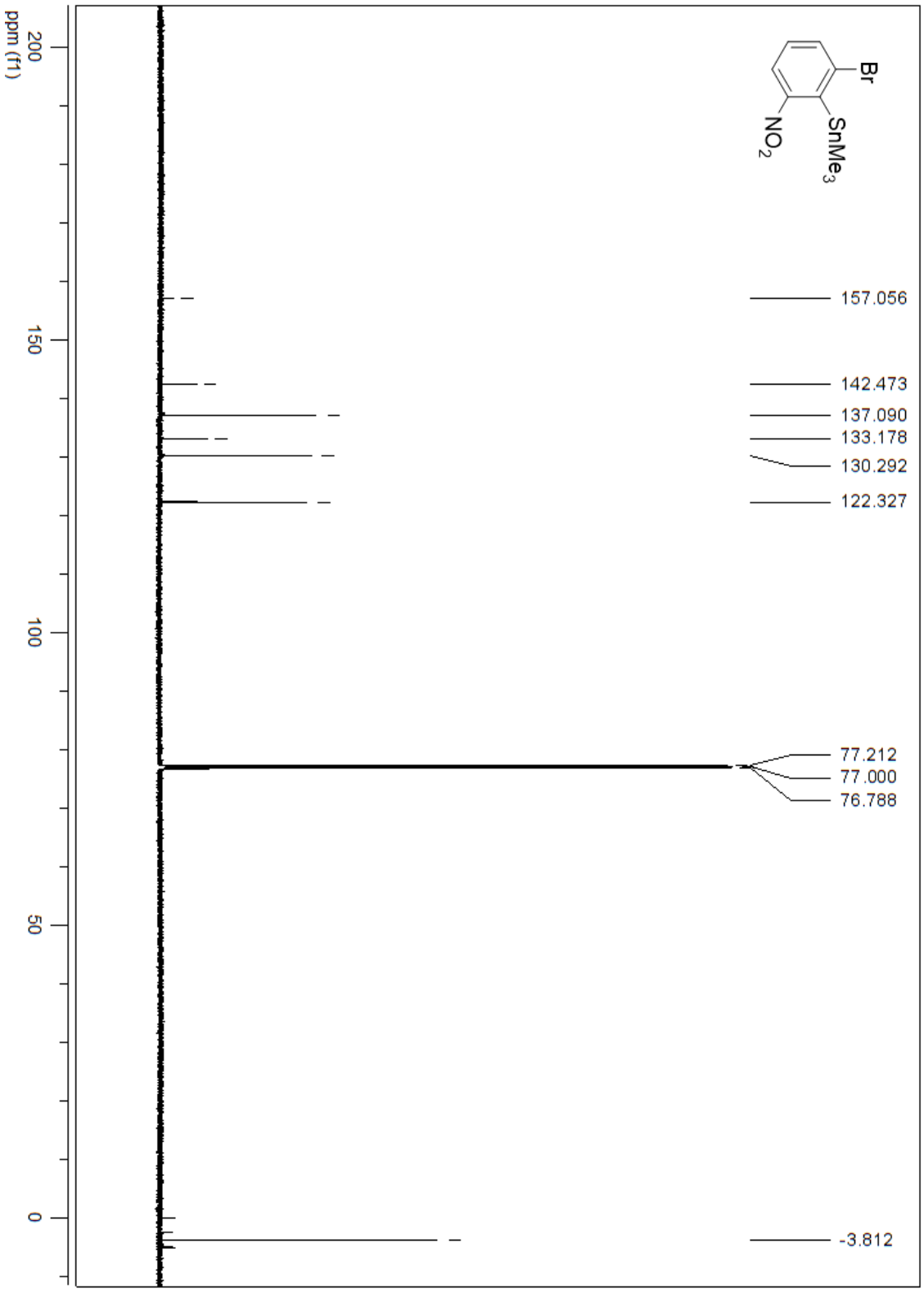

Figure 74: ^{13}C NMR of (2-bromo-6-nitro-phenyl)-trimethyl-stannane **(50)**

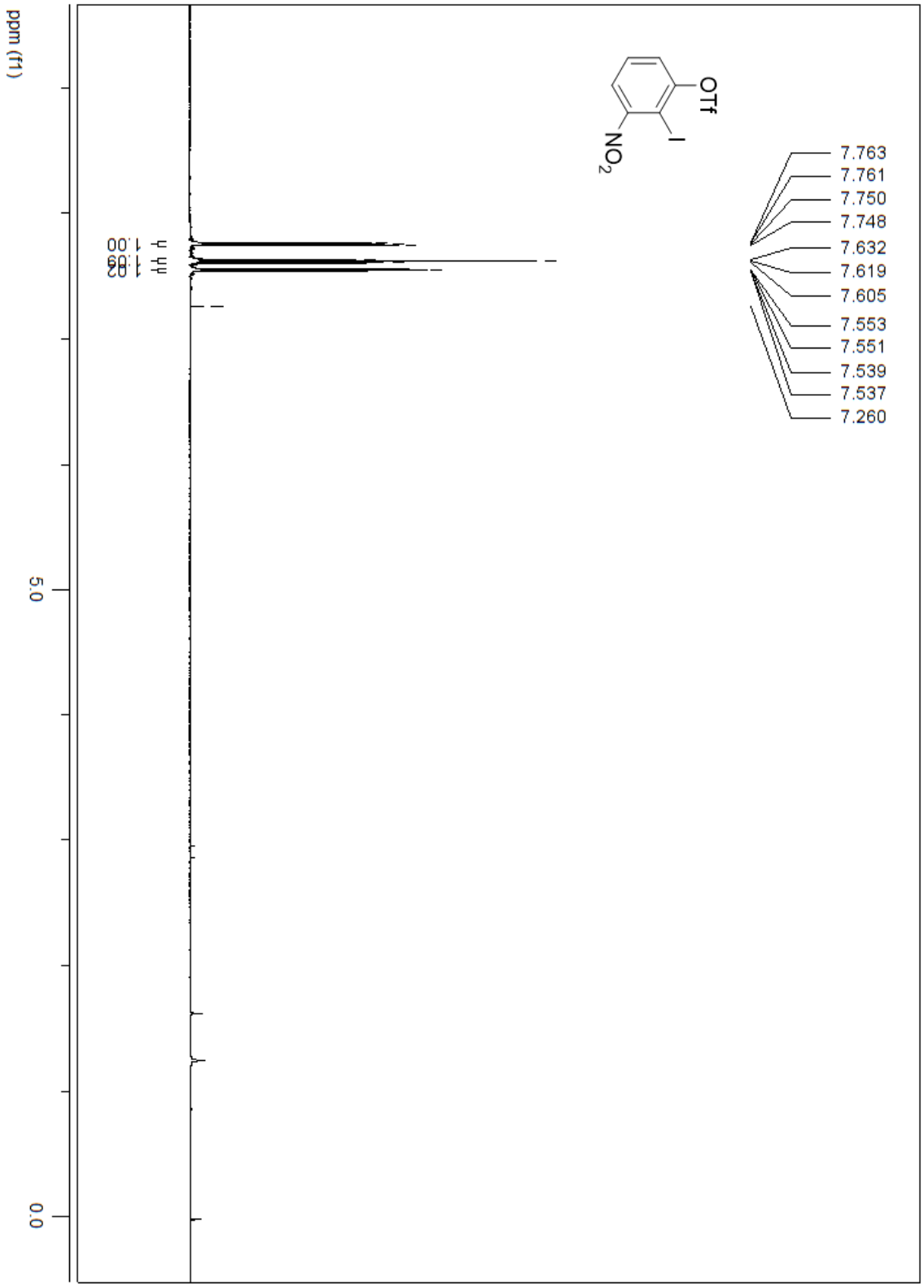

Figure 75: ^{1}H NMR of trifluoro-methanesulfonic acid 2-iodo-3-nitro-phenyl ester **(52)**

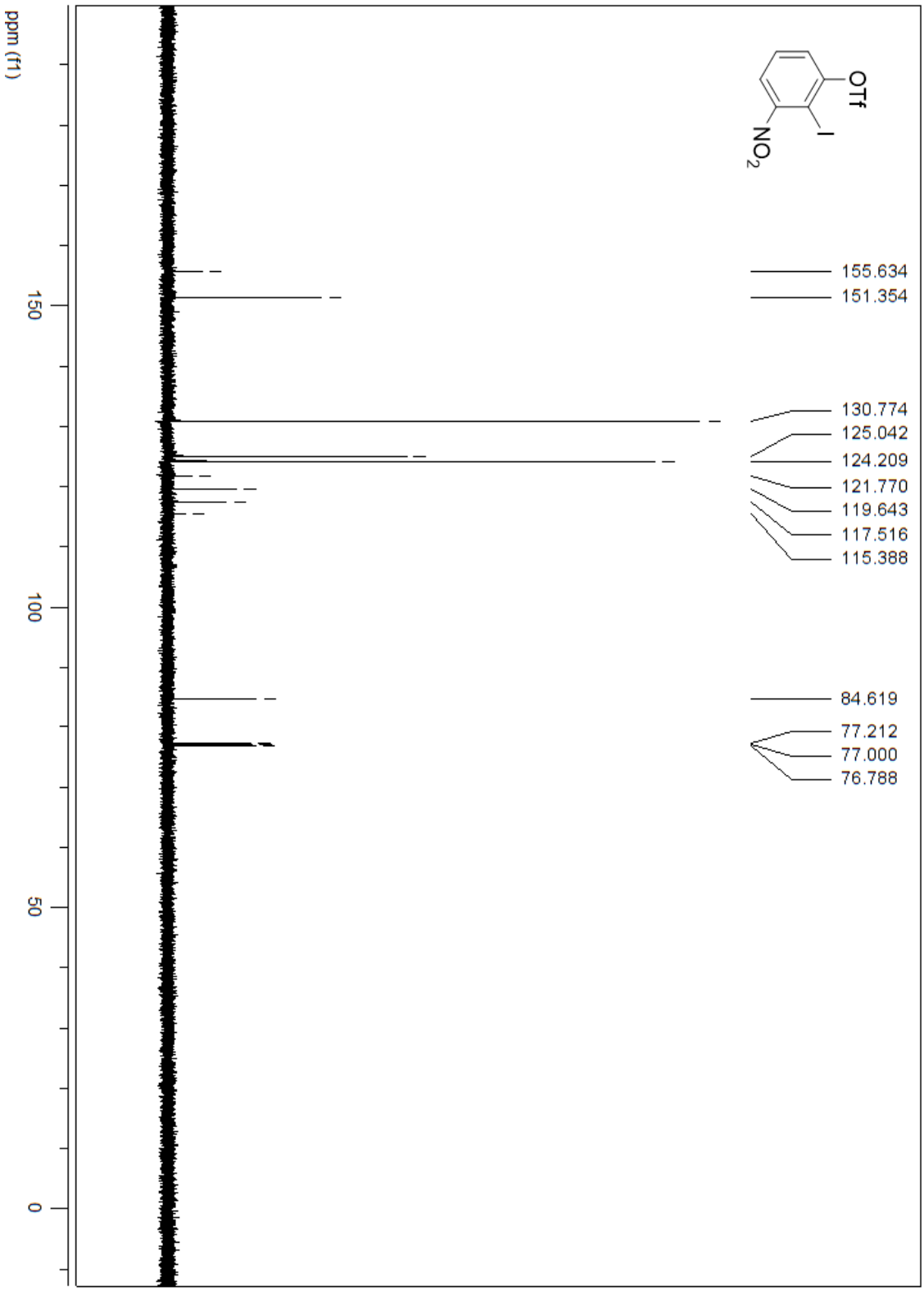

Figure 76: ^{13}C NMR trifluoro-methanesulfonic acid 2-iodo-3-nitro-phenyl ester **(52)**

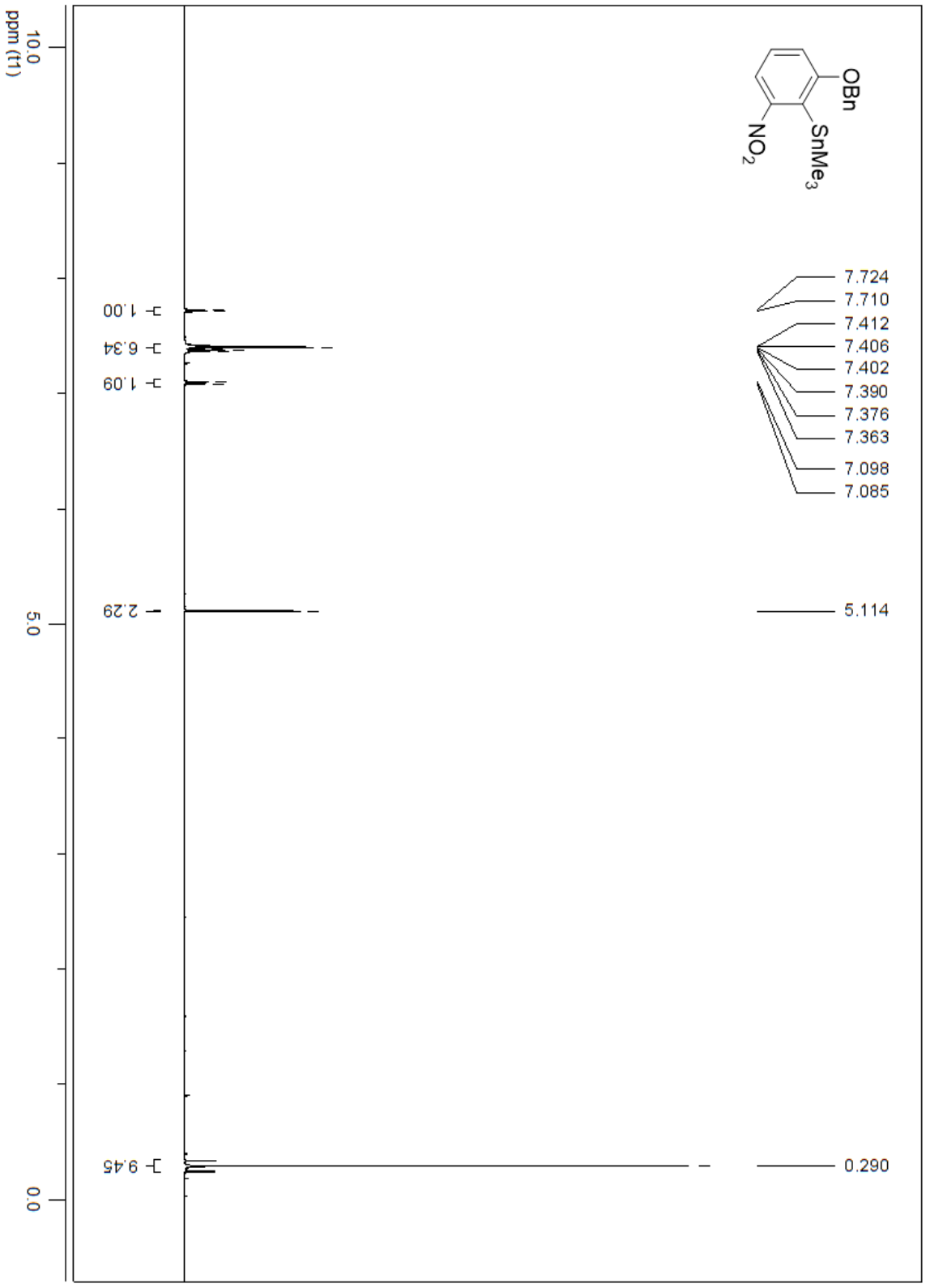

Figure 77: ^{1}H NMR of (2-benzyloxy-6-nitro-phenyl)-trimethyl-stannane **(56)**

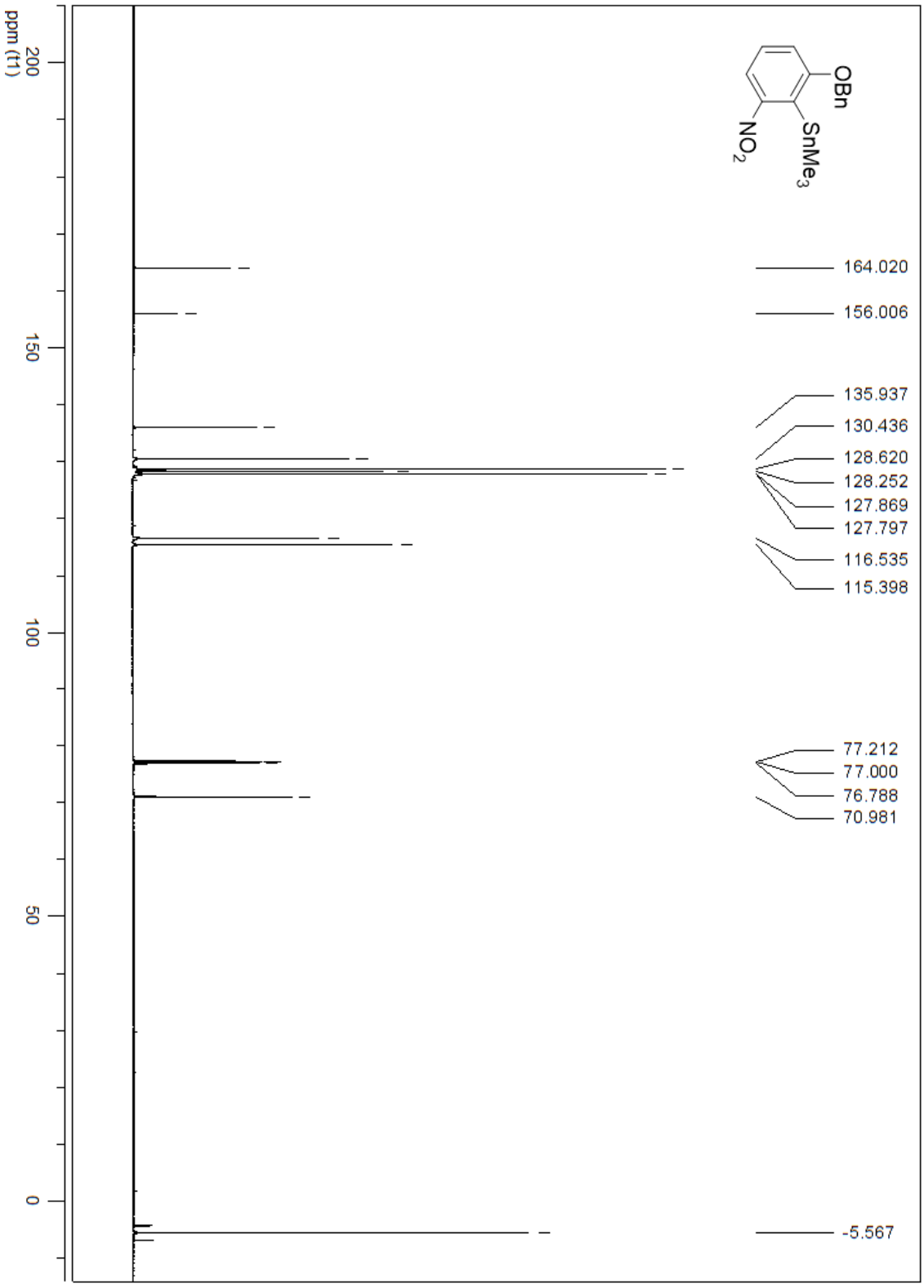

Figure 78: ^{13}C NMR of (2-benzyloxy-6-nitro-phenyl)-trimethyl-stannane **(56)**

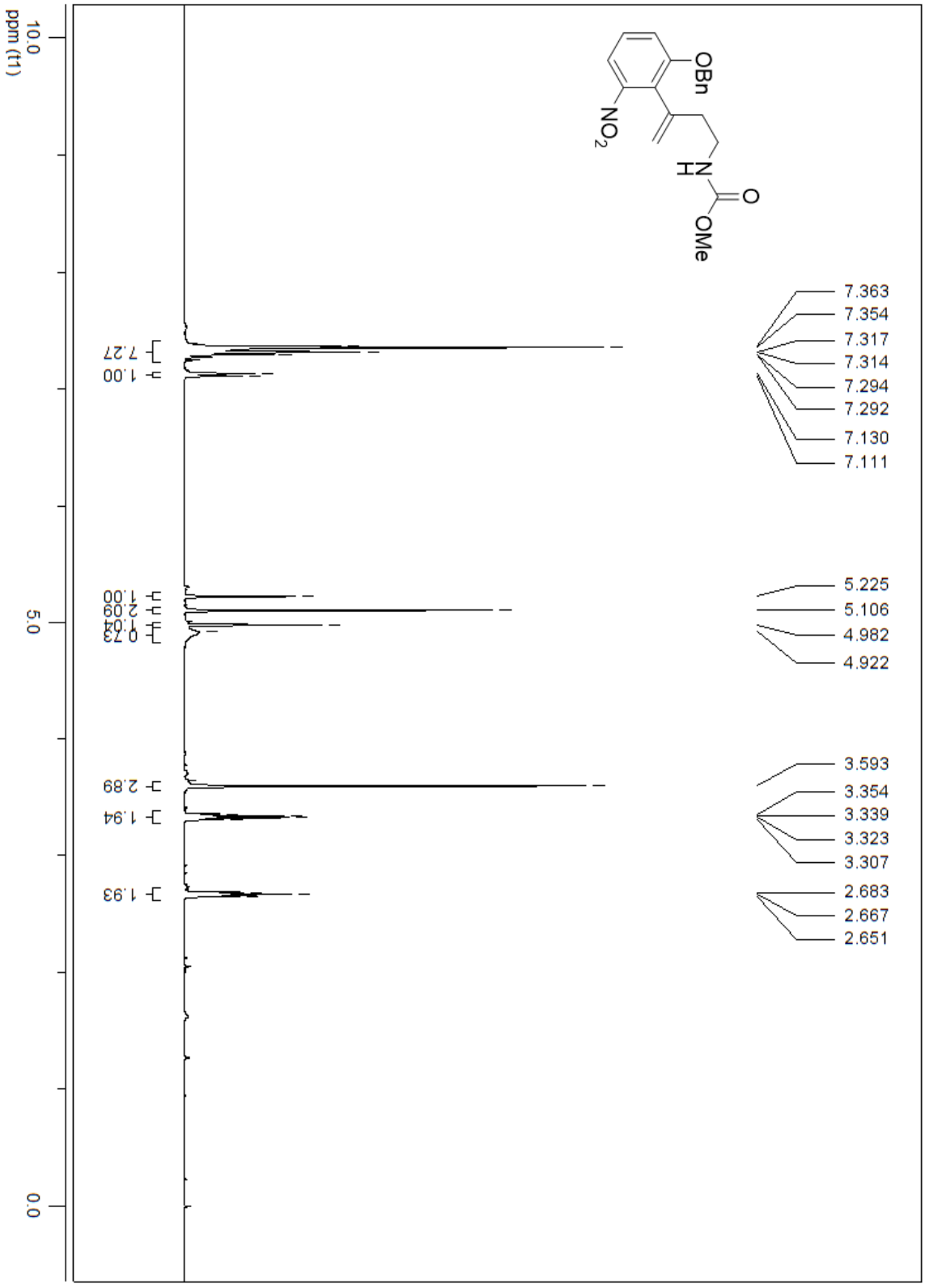

Figure 79: ^{1}H NMR (65 ^{o}C) of [3-(2-benzyloxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester **(57)**

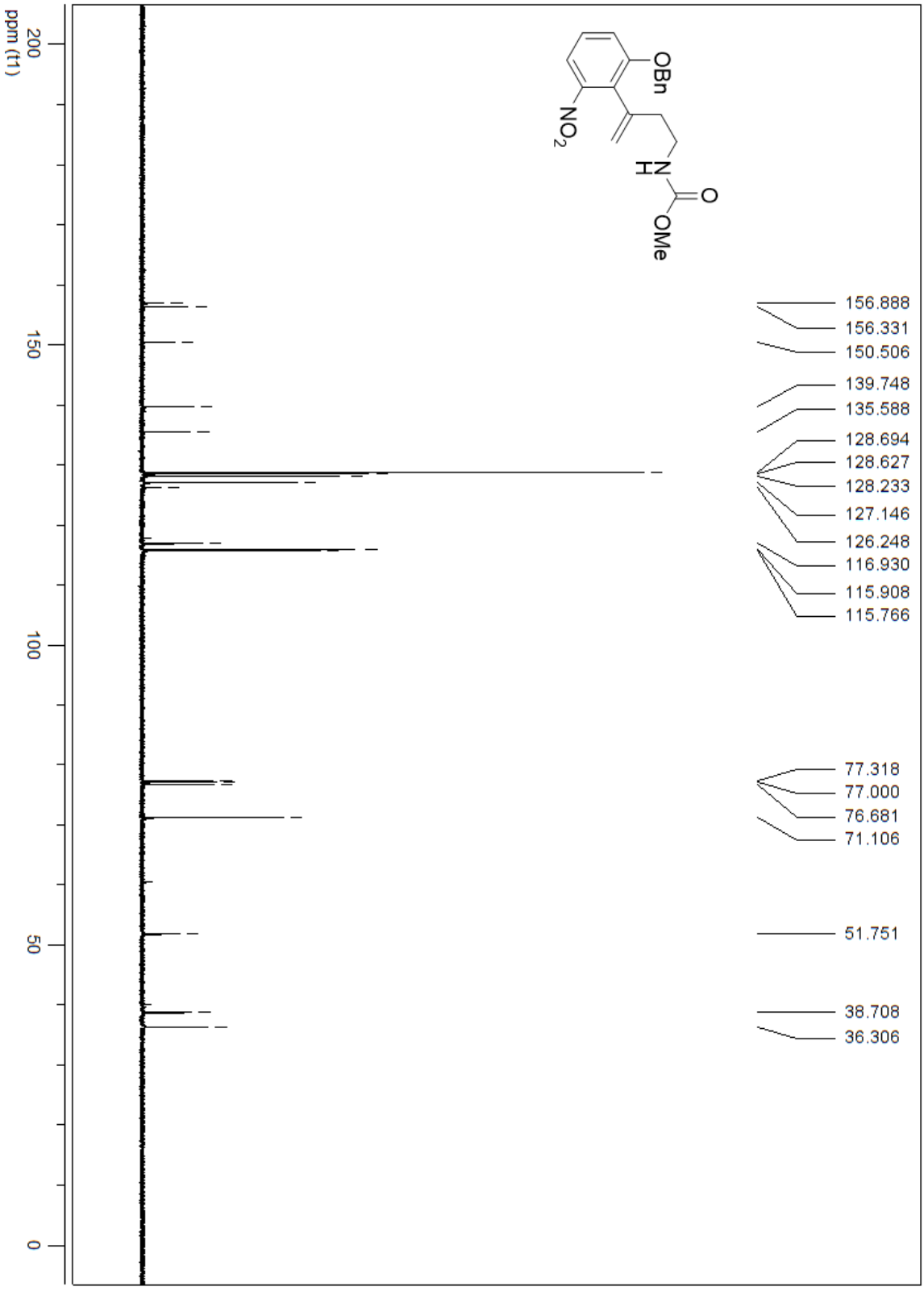

Figure 80: ^{13}C of[3-(2-benzyloxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester **(57)**

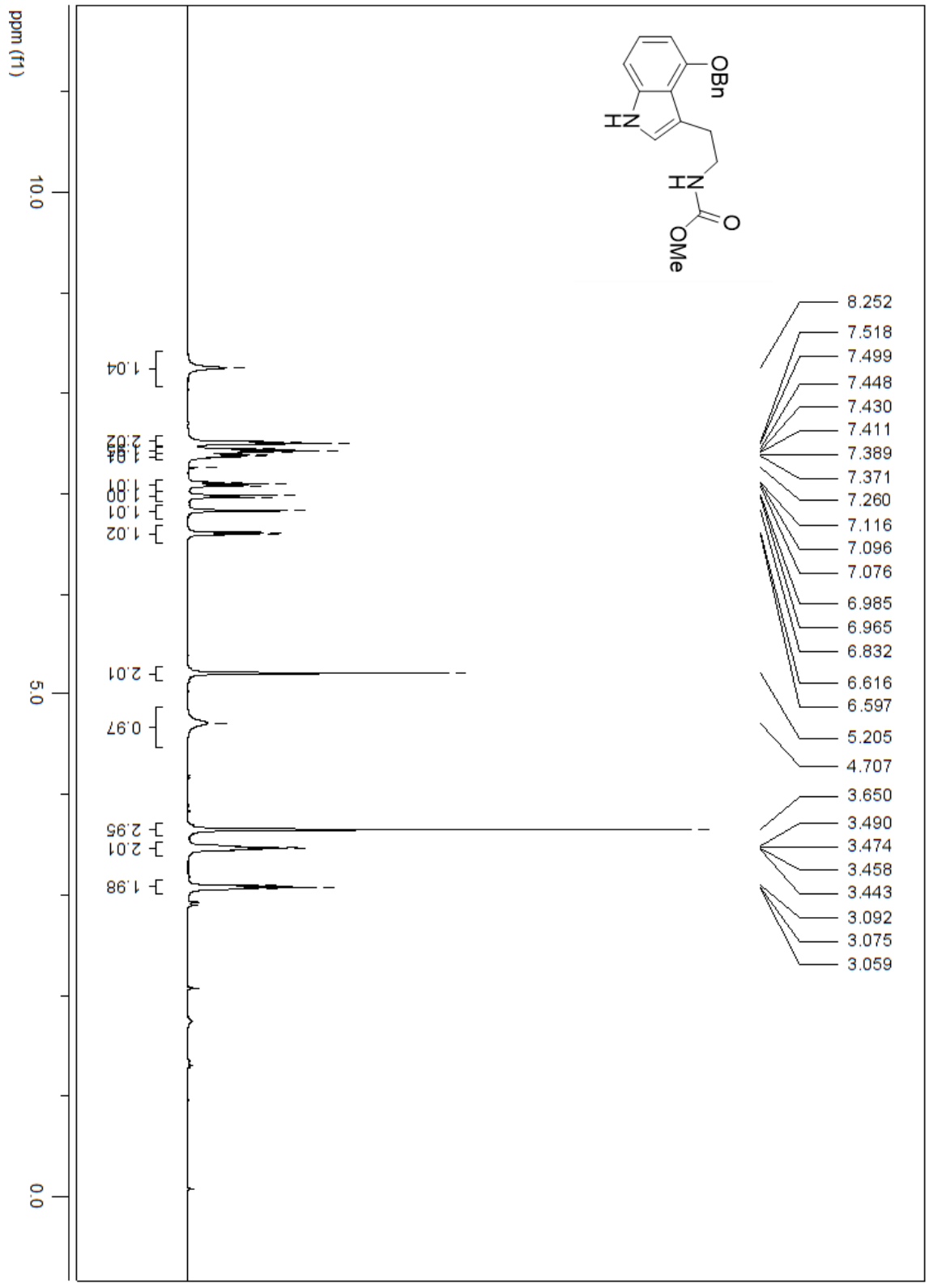

Figure 81: ^{1}H NMR (65 ^{o}C) of [2-(4-benzyloxy-1H-indol-3-yl)-ethyl]-carbamic acid methyl ester **(58)**

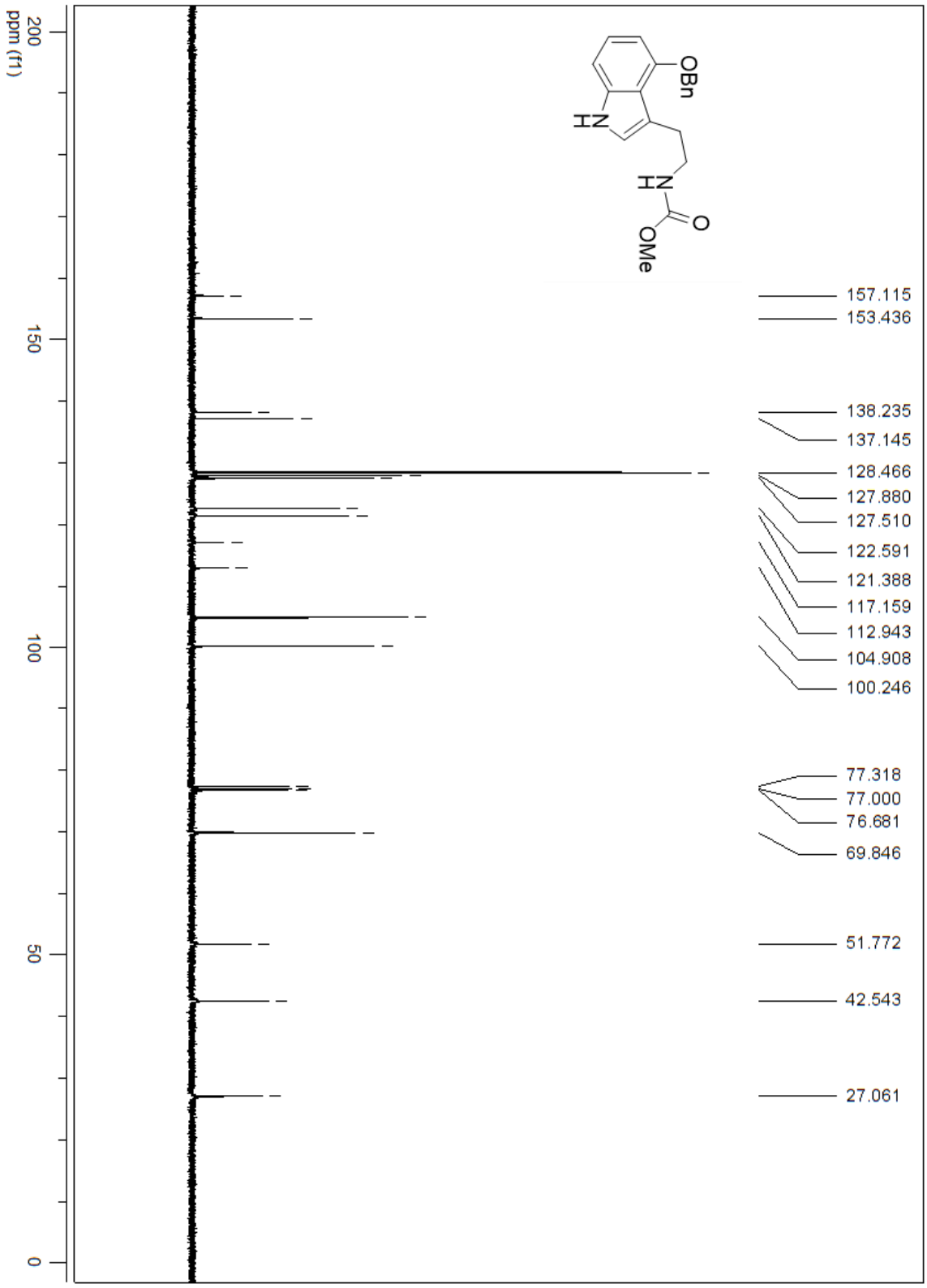

Figure 82: ^{13}C NMR of [2-(4-benzyloxy-1H-indol-3-yl)-ethyl]-carbamic acid methyl ester **(58)**

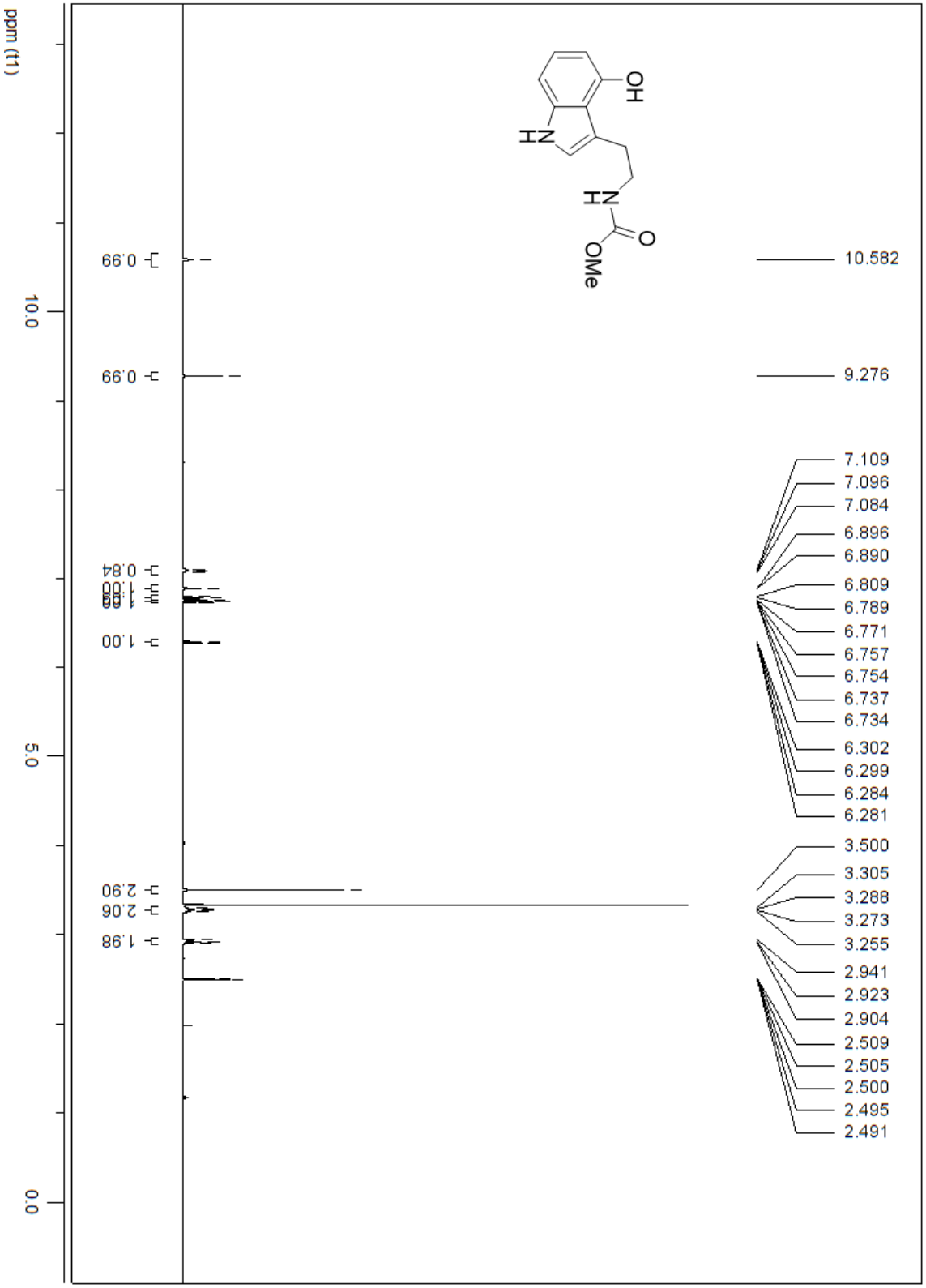

Figure 83: ^{1}H NMR of [2-(4-hydroxy-1H-indol-3-yl)-ethyl]-carbamic acid methyl ester **(59)**

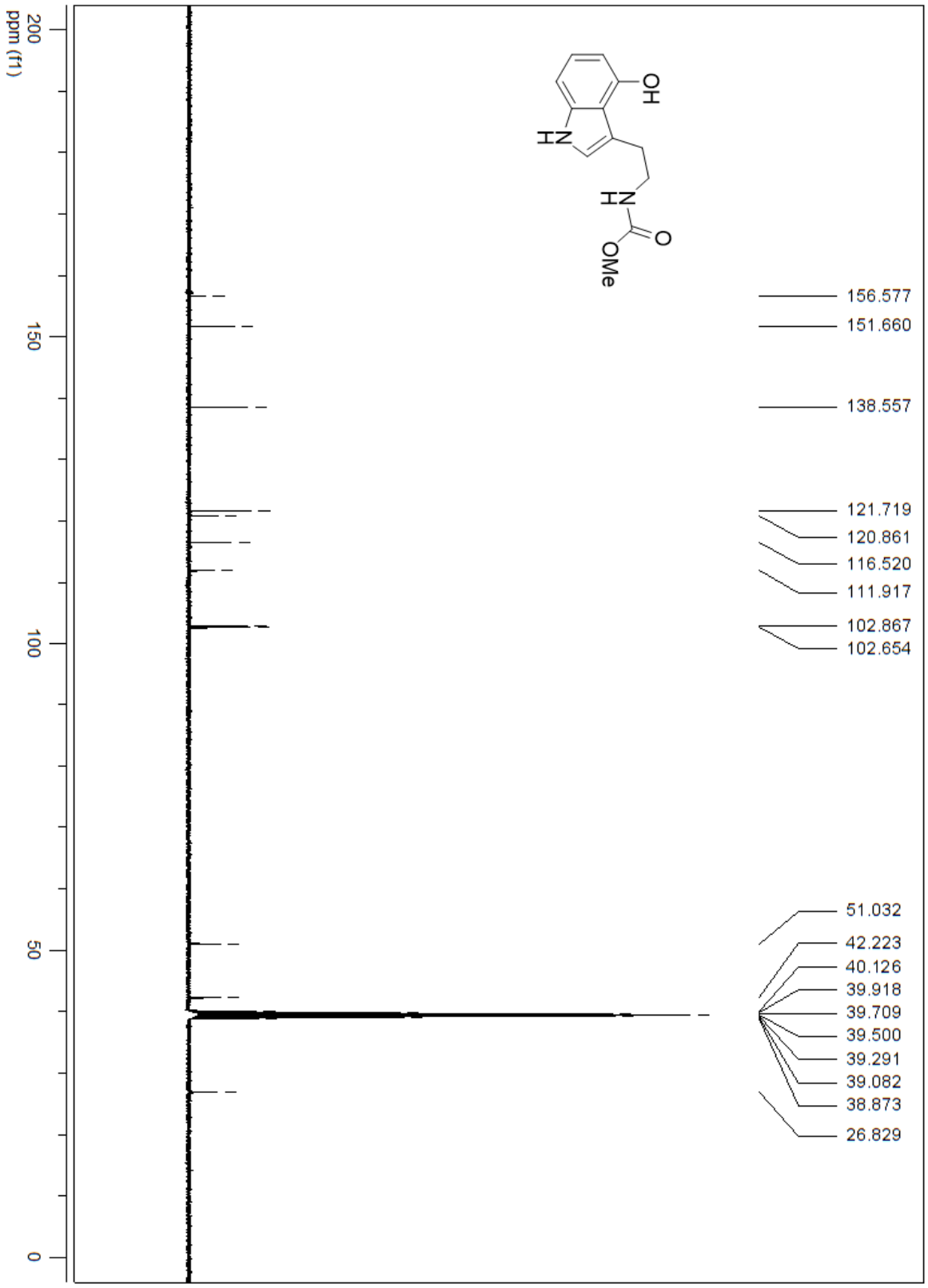

Figure 84: ^{13}C NMR of [2-(4-hydroxy-1H-indol-3-yl)-ethyl]-carbamic acid methyl ester **(59)**

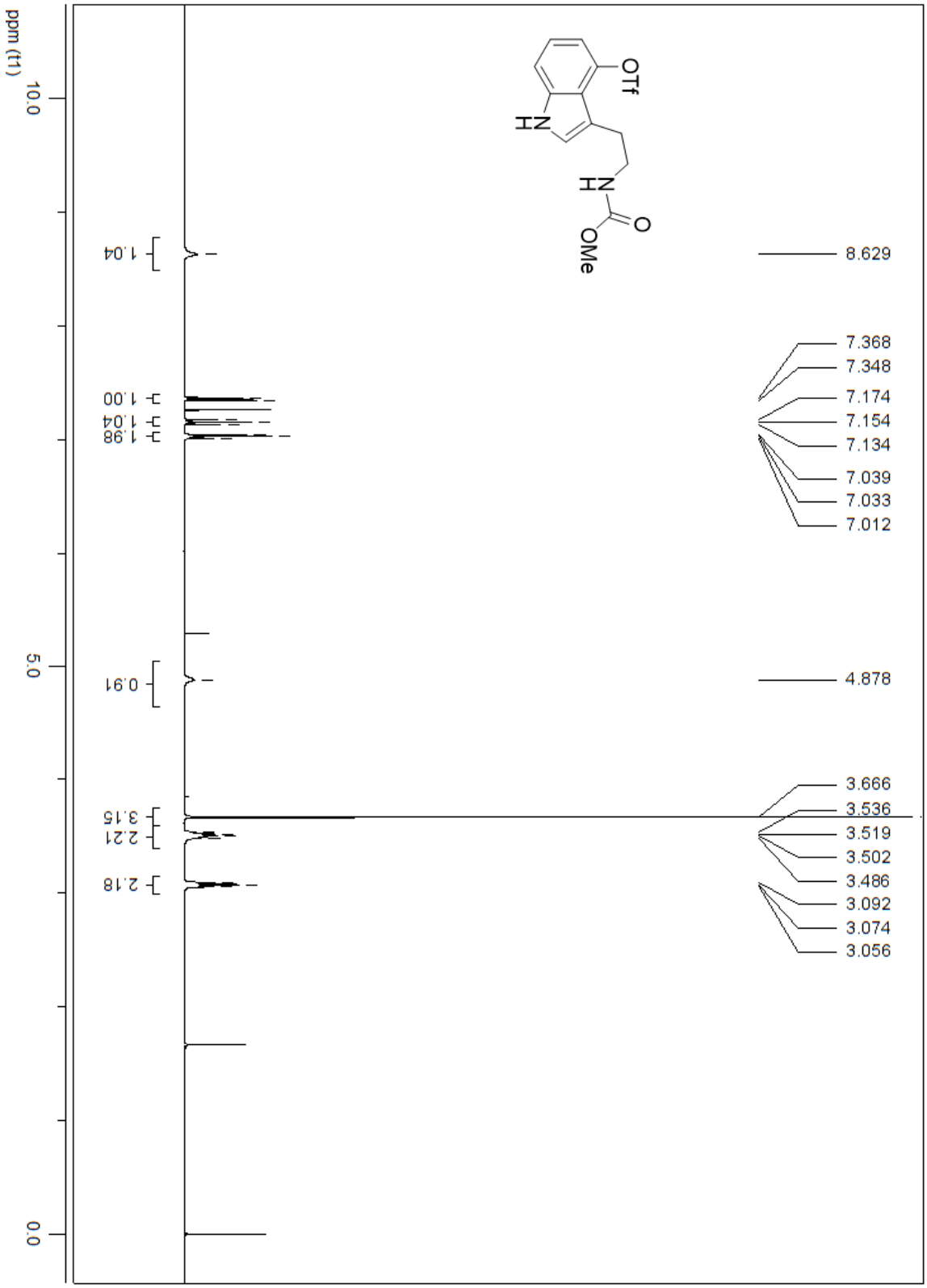

Figure 85: ^{1}H NMR of trifluoro-methanesulfonic acid 3-(2-methoxycarbonylamino-ethyl)-1H-indol-4-yl ester **(60)**

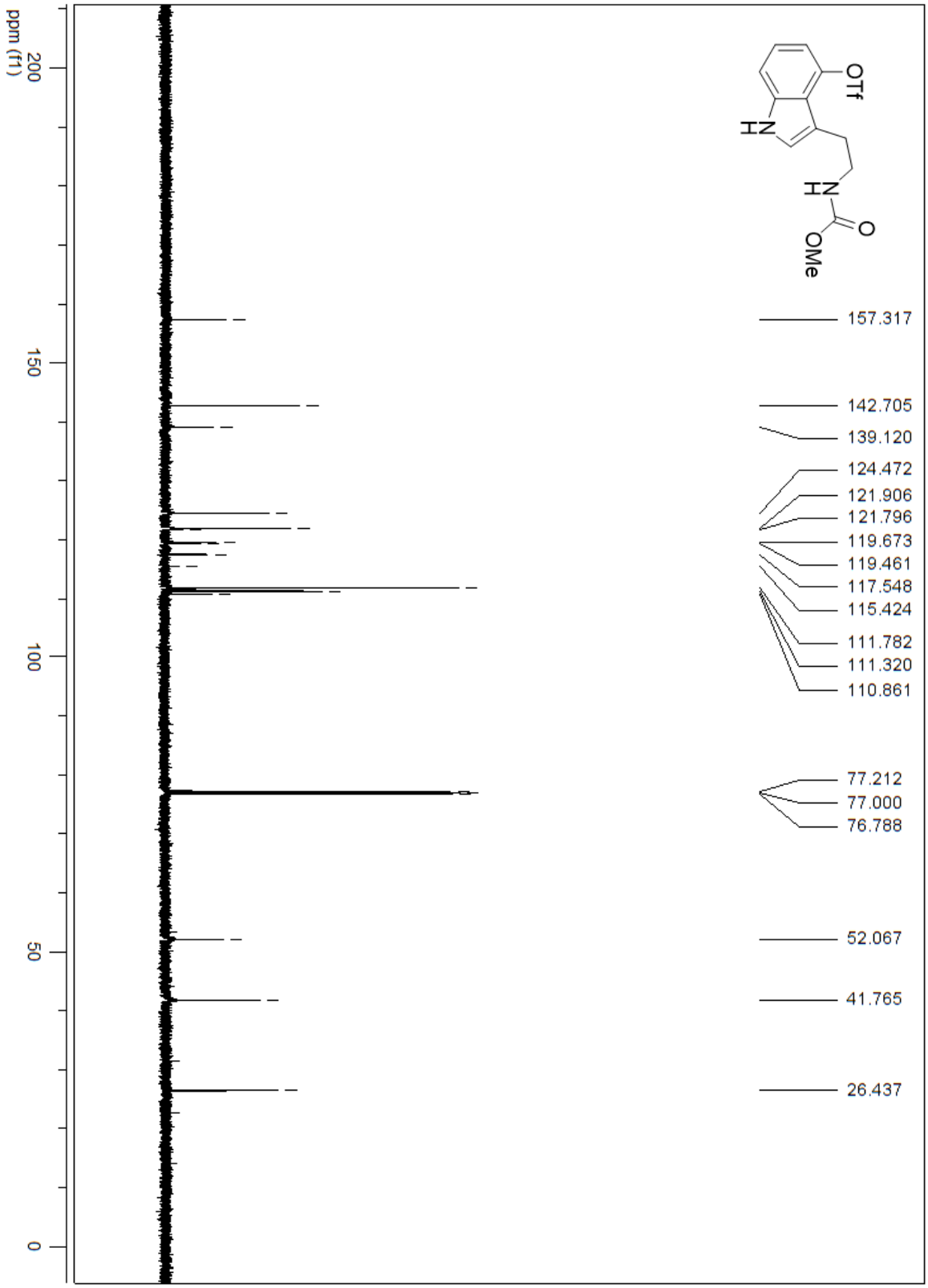

Figure 86: ^{13}C NMR of trifluoro-methanesulfonic acid 3-(2-methoxycarbonylamino-ethyl)-1H-indol-4-yl ester **(60)**

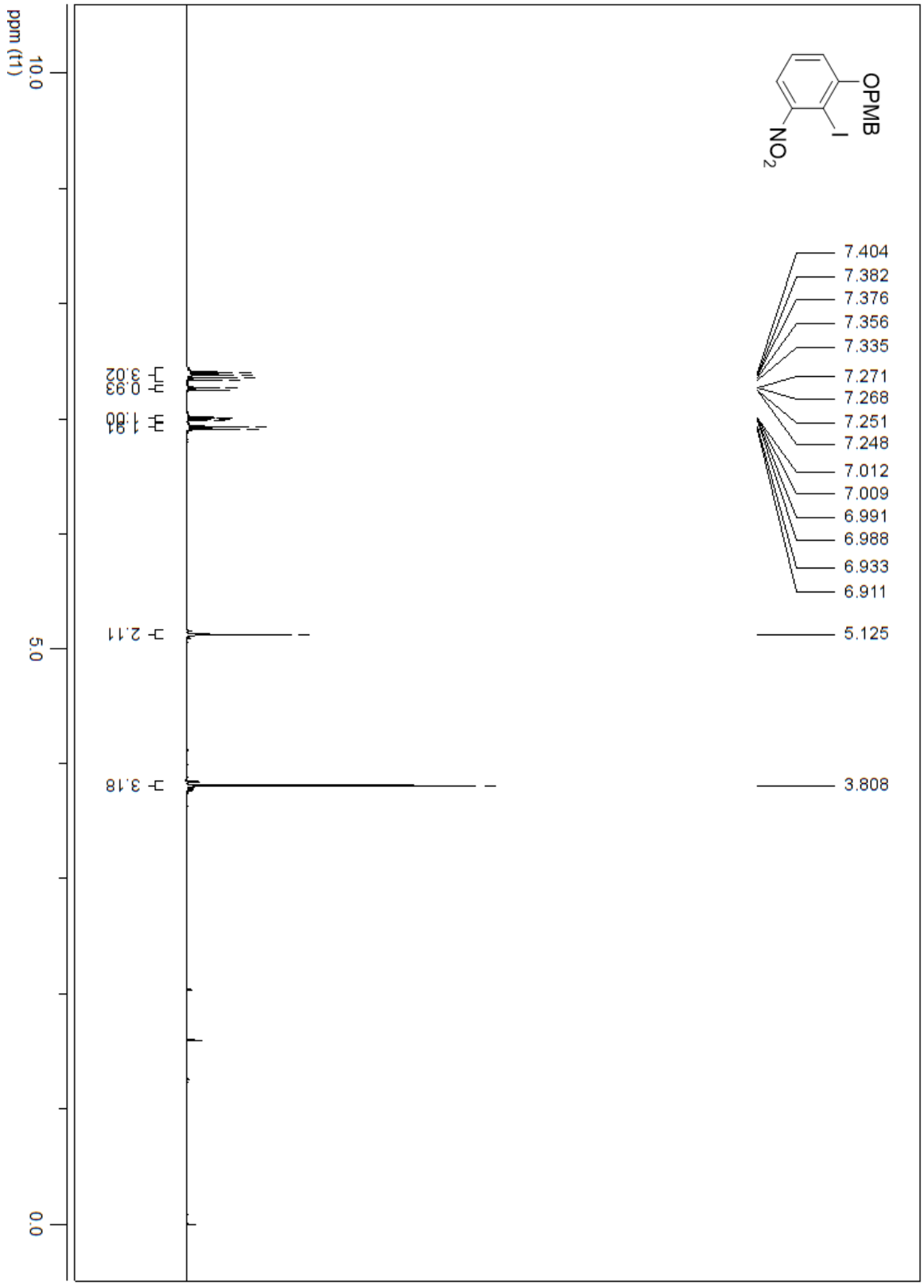

Figure 87: ^{1}H NMR of 2-iodo-1-(4-methoxy-benzyloxy)-3-nitro-benzene **(63)**

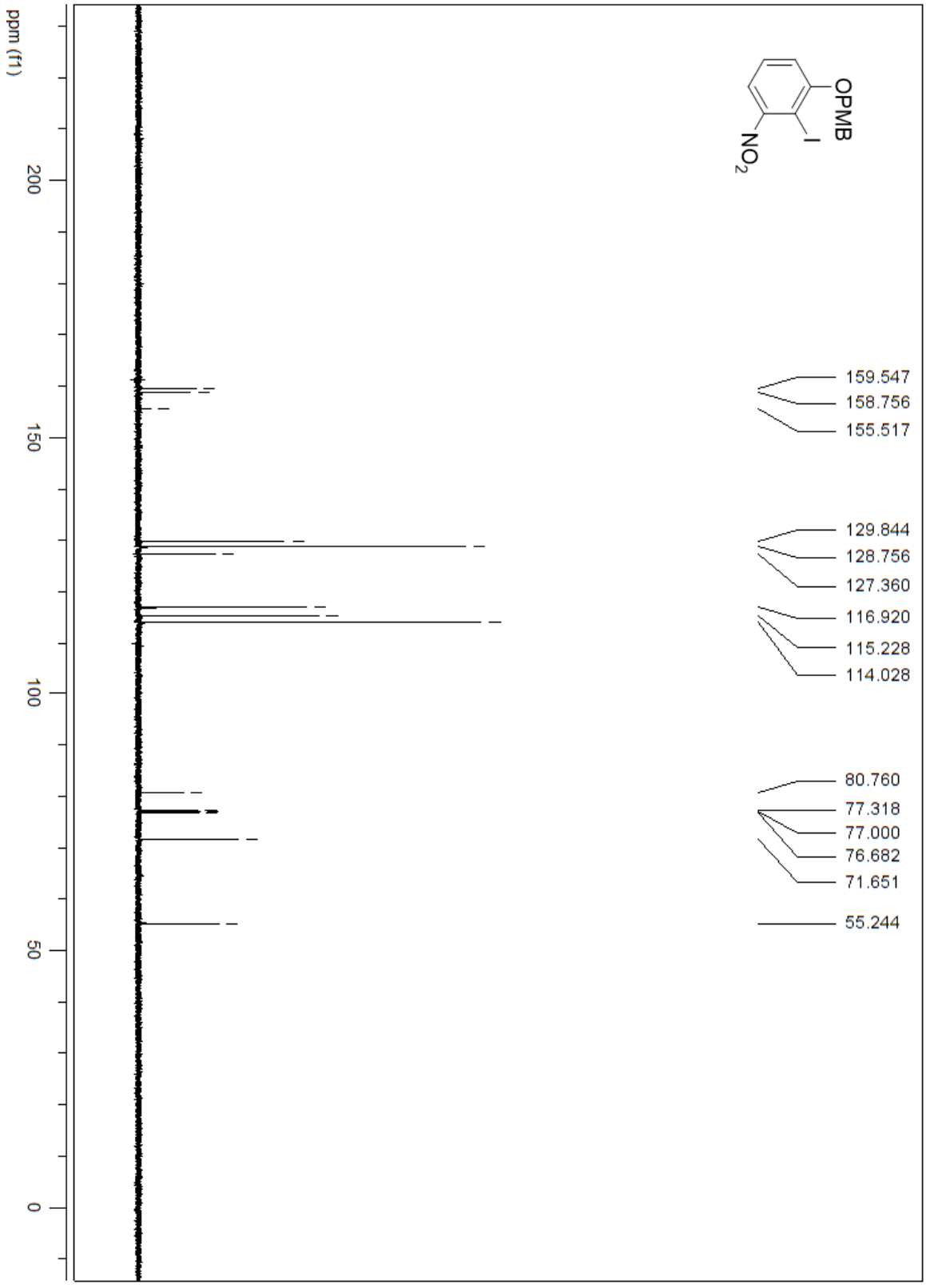

Figure 88: ^{13}C NMR 2-iodo-1-(4-methoxy-benzyloxy)-3-nitro-benzene **(63)**

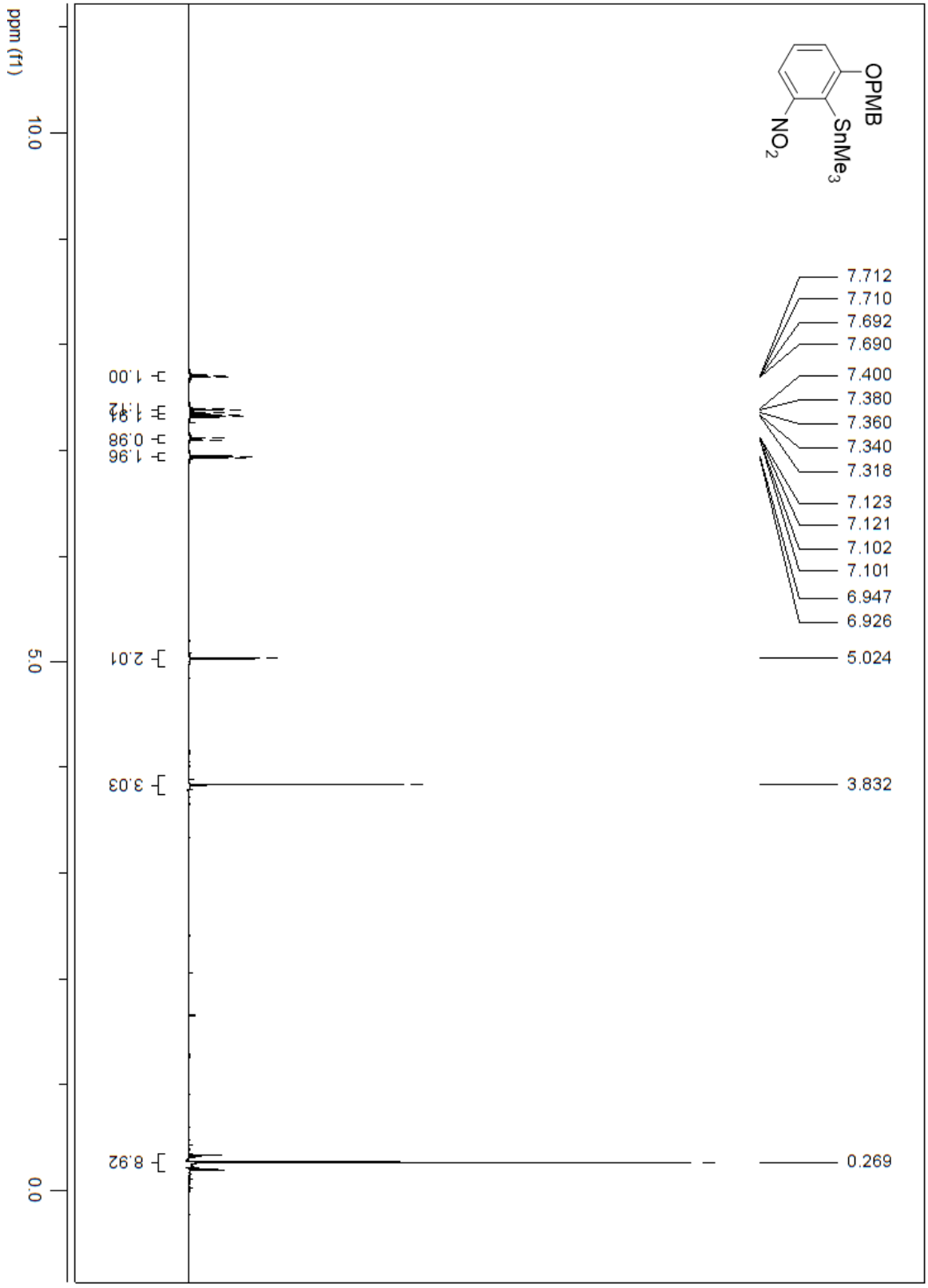

Figure 89: ^{1}H NMR of [2-(4-methoxy-benzyloxy)-6-nitro-phenyl]-trimethyl-stannane **(64)**

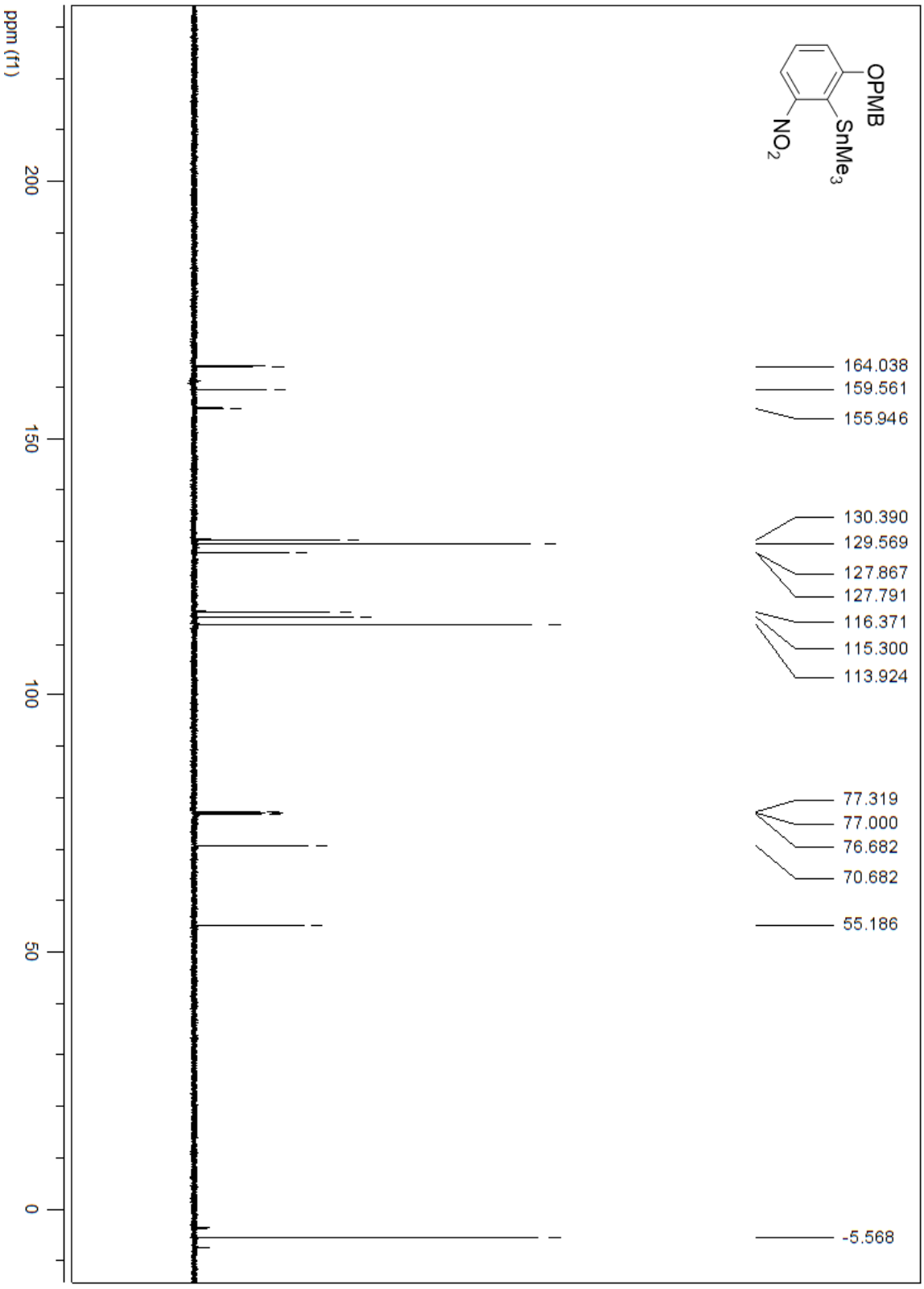

Figure 90: ^{13}C NMR of [2-(4-methoxy-benzyloxy)-6-nitro-phenyl]-trimethyl-stannane **(64)**

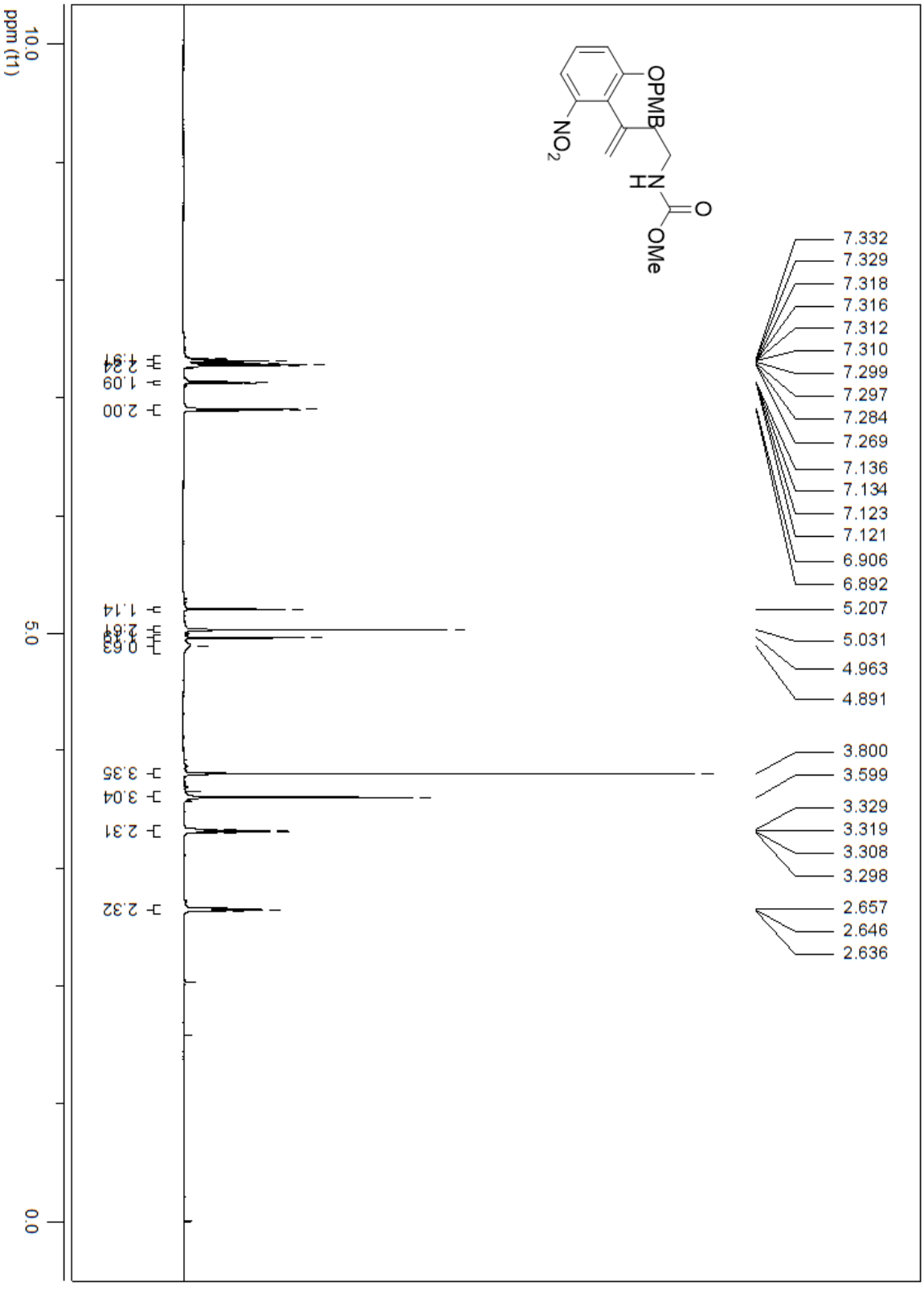

Figure 91: ^{1}H NMR (65 ^{o}C) of {3-[2-(4-methoxy-benzyloxy)-6-nitro-phenyl]-but-3-enyl}-carbamic acid methyl ester **(65)**

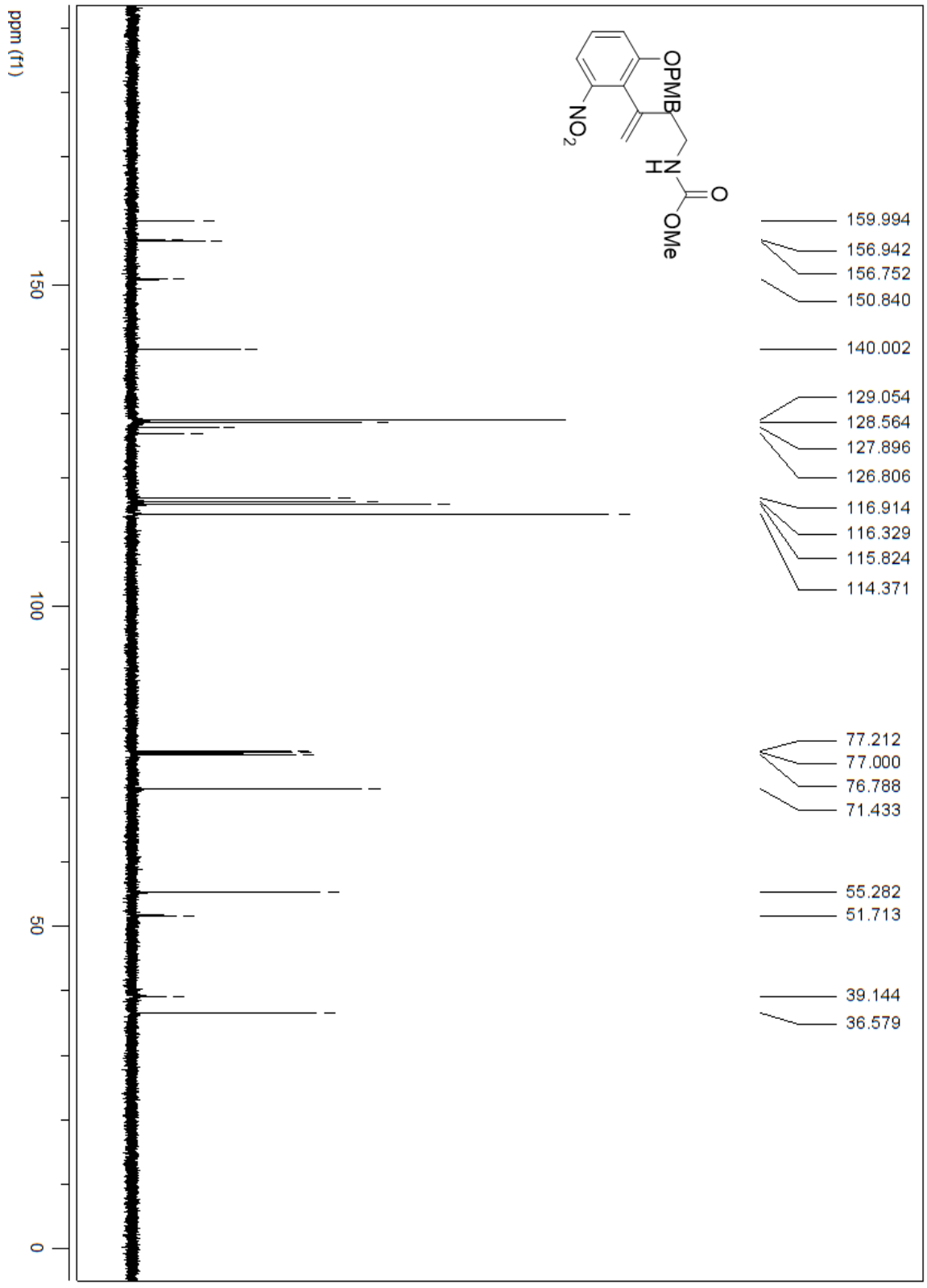

Figure 92: ^{13}C NMR (65^{o}C) of {3-[2-(4-methoxy-benzyloxy)-6-nitro-phenyl]-but-3-enyl}-carbamic acid methyl ester **(65)**

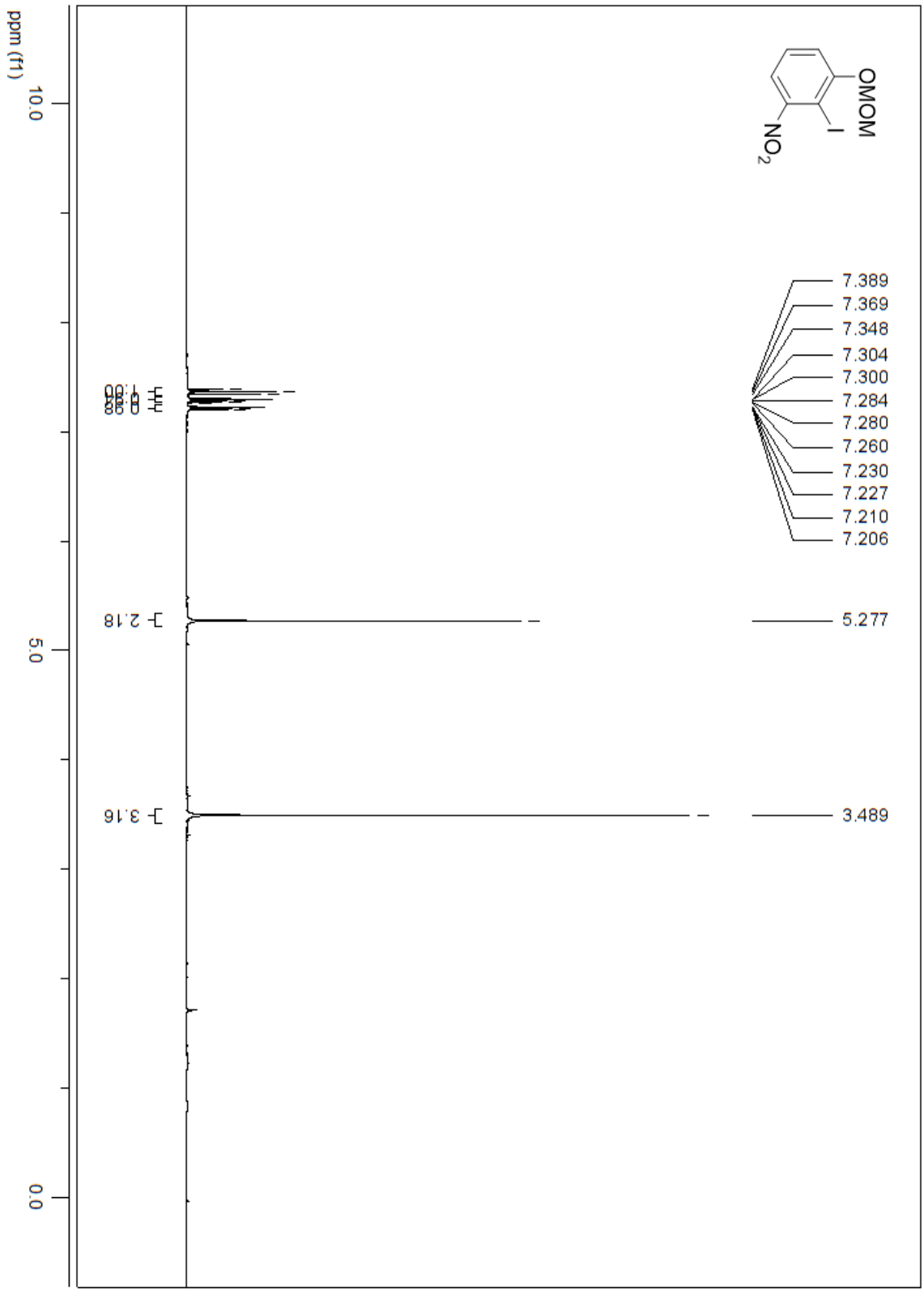

Figure 93: ^{1}H NMR of 2-iodo-1-methoxymethoxy-3-nitro-benzene **(66)**

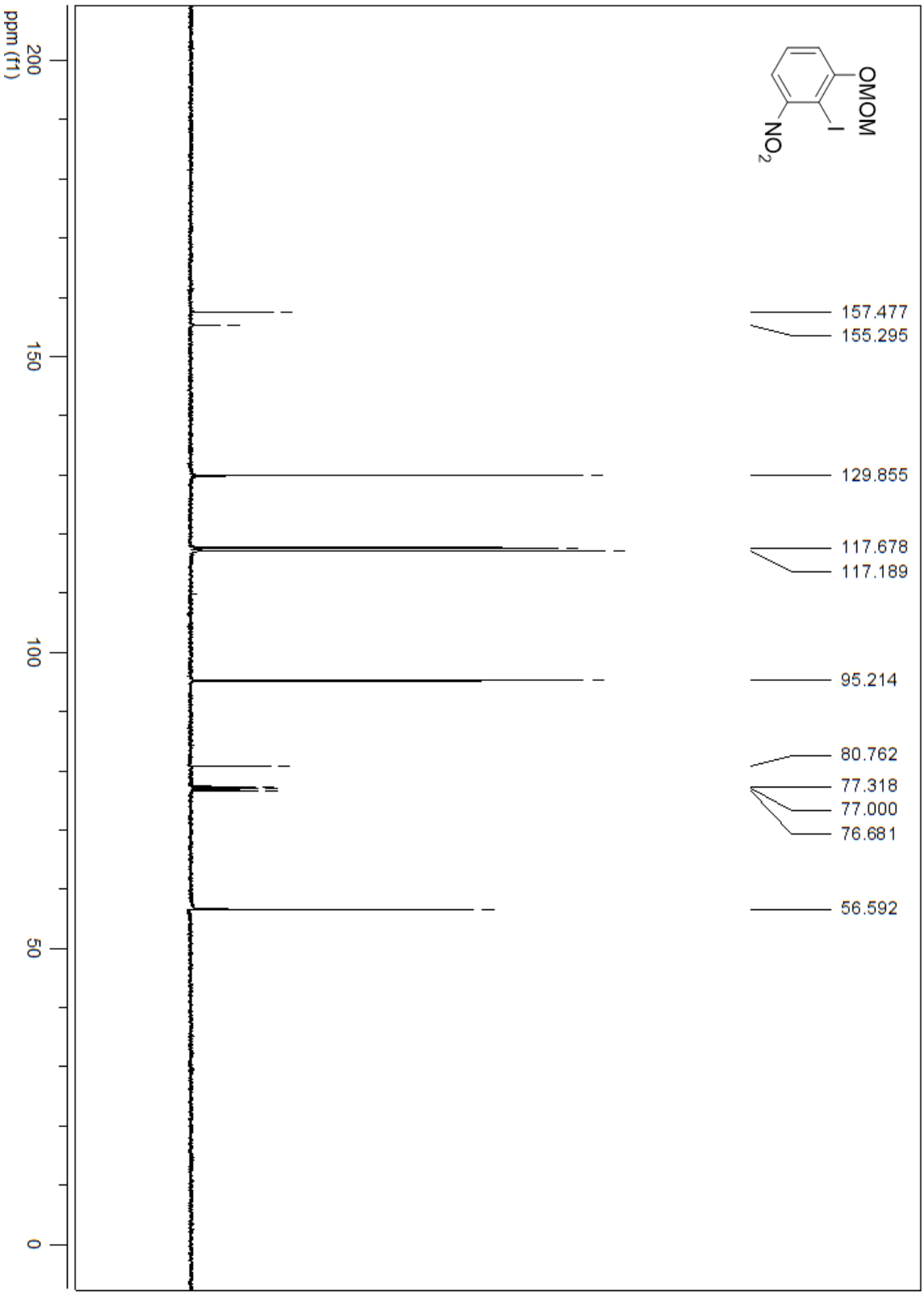

Figure 94: ^{13}C NMR of 2-iodo-1-methoxymethoxy-3-nitro-benzene **(66)**

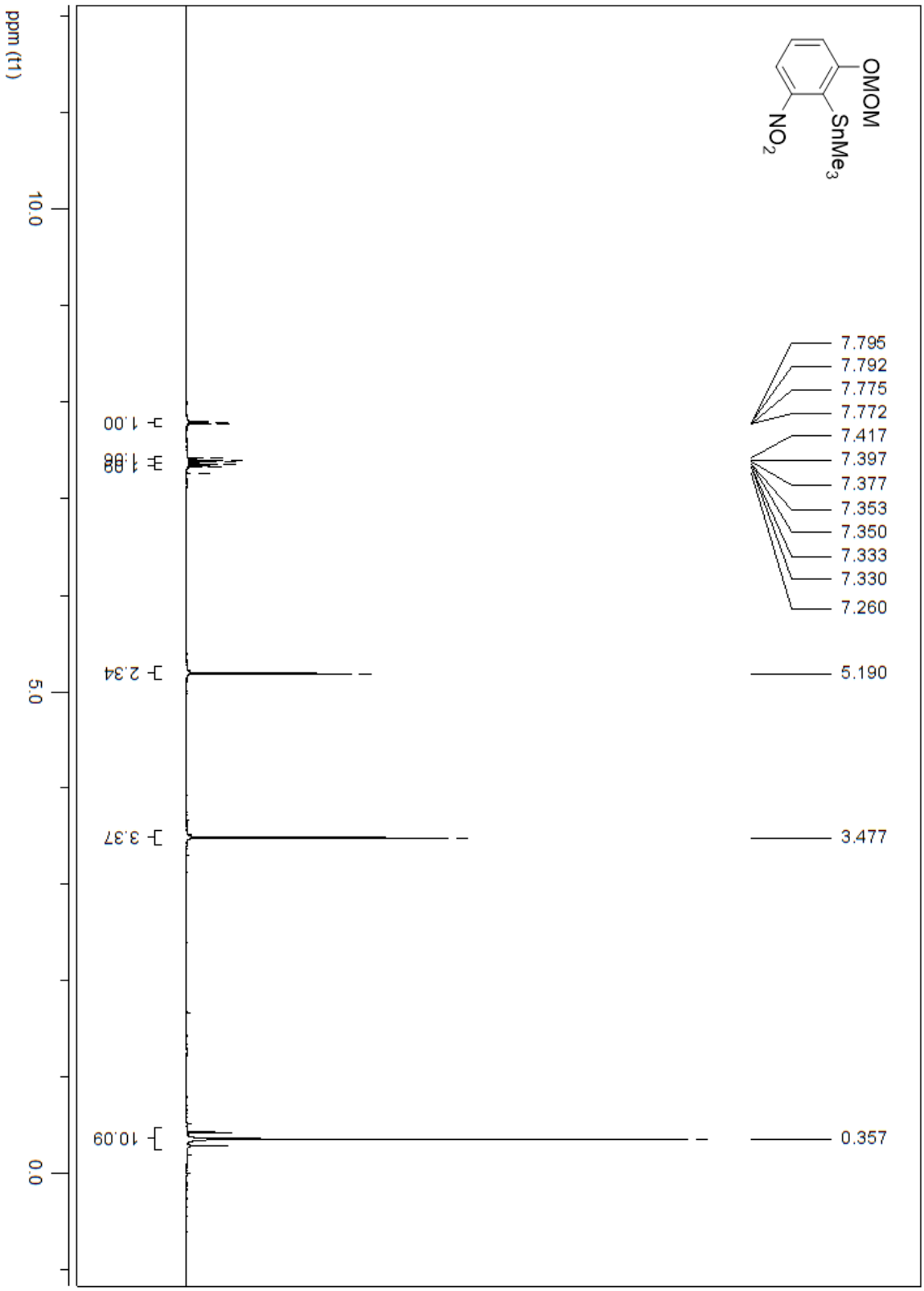

Figure 95: ^{1}H NMR of (2-methoxymethoxy-6-nitro-phenyl)-trimethyl-stannane **(67)**

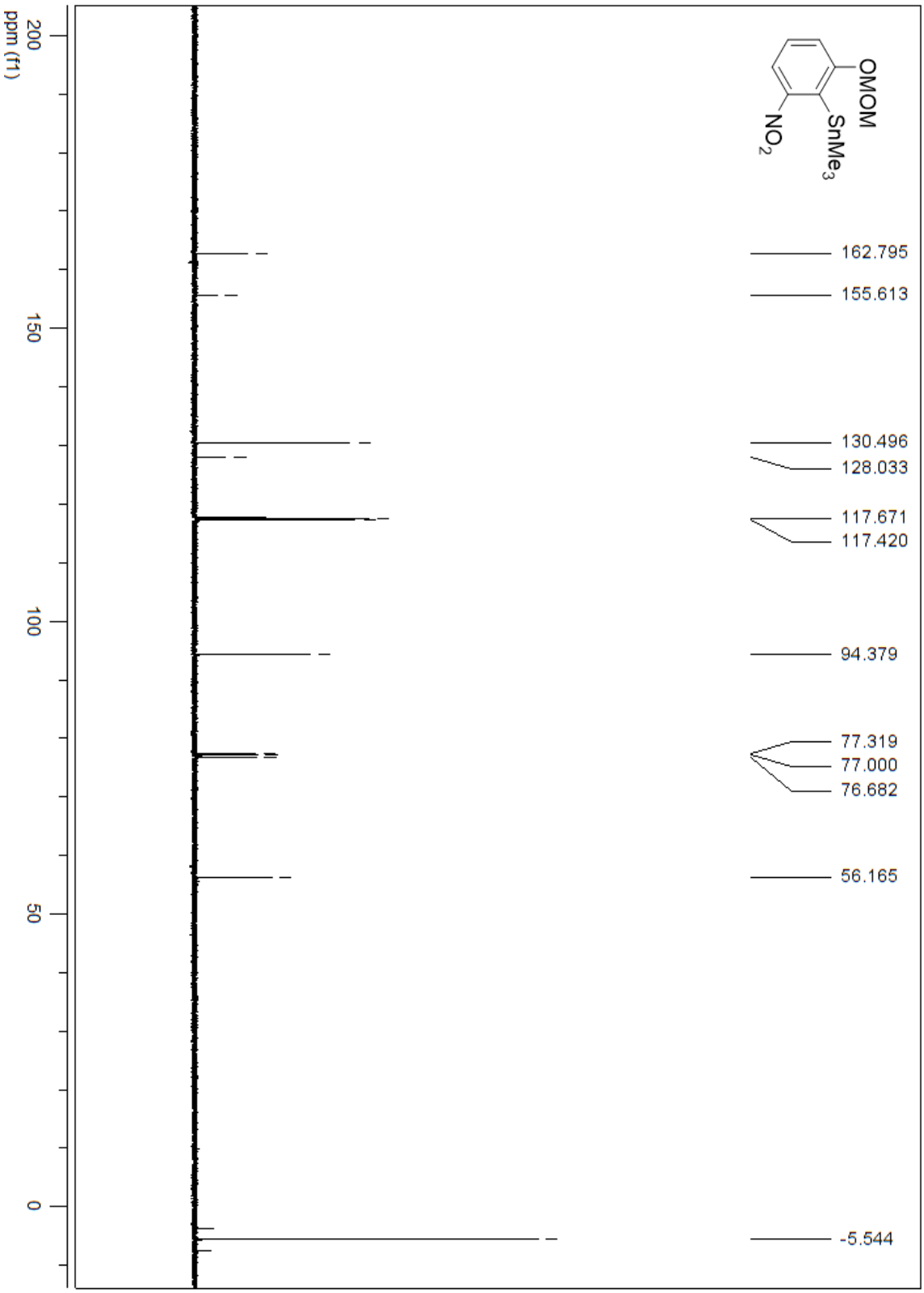

Figure 96: ^{13}C NMR of (2-methoxymethoxy-6-nitro-phenyl)-trimethyl-stannane **(67)**

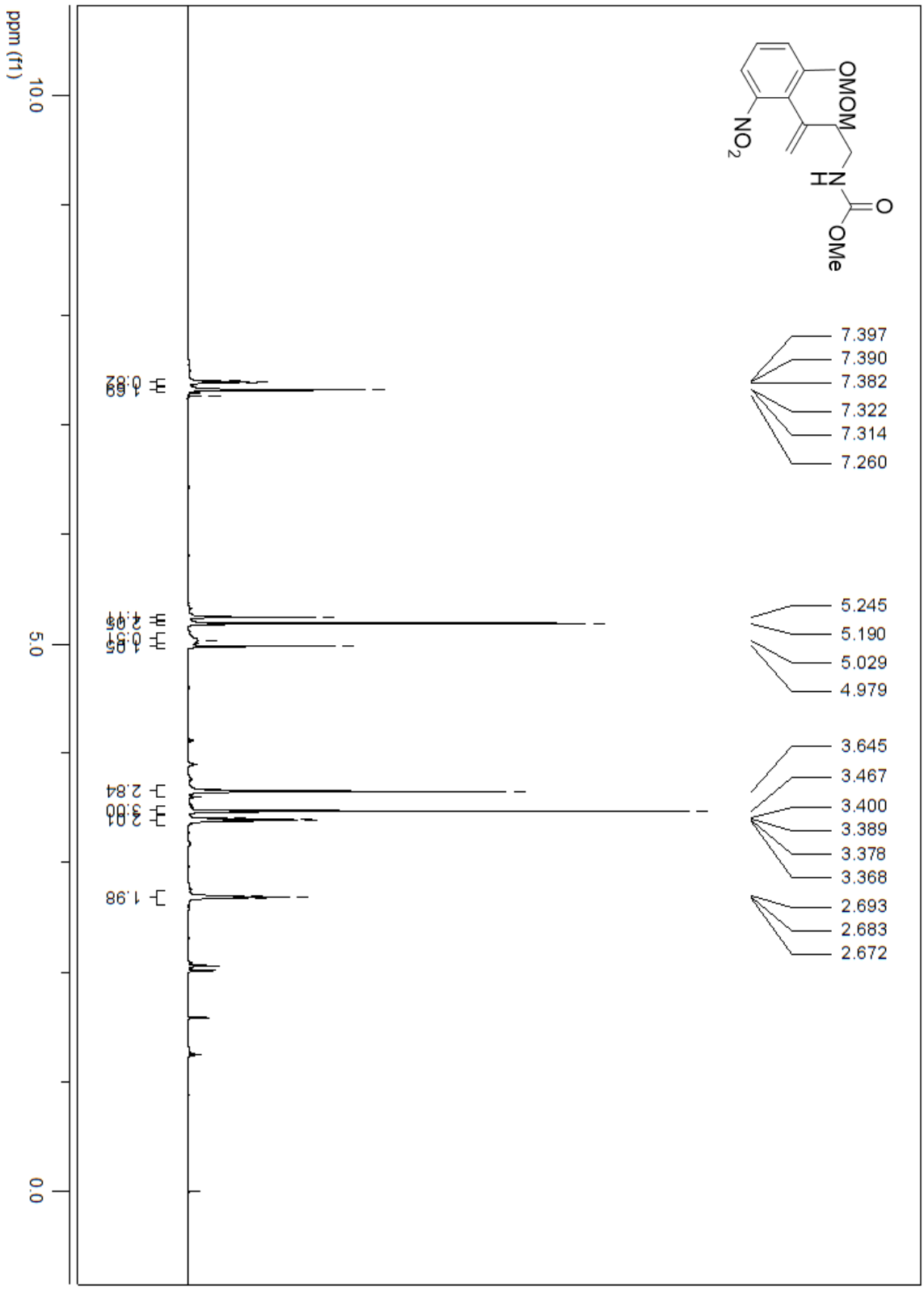

Figure 97: ^{1}H NMR (65^{o}C) of [3-(2-methoxymethoxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester **(68)**

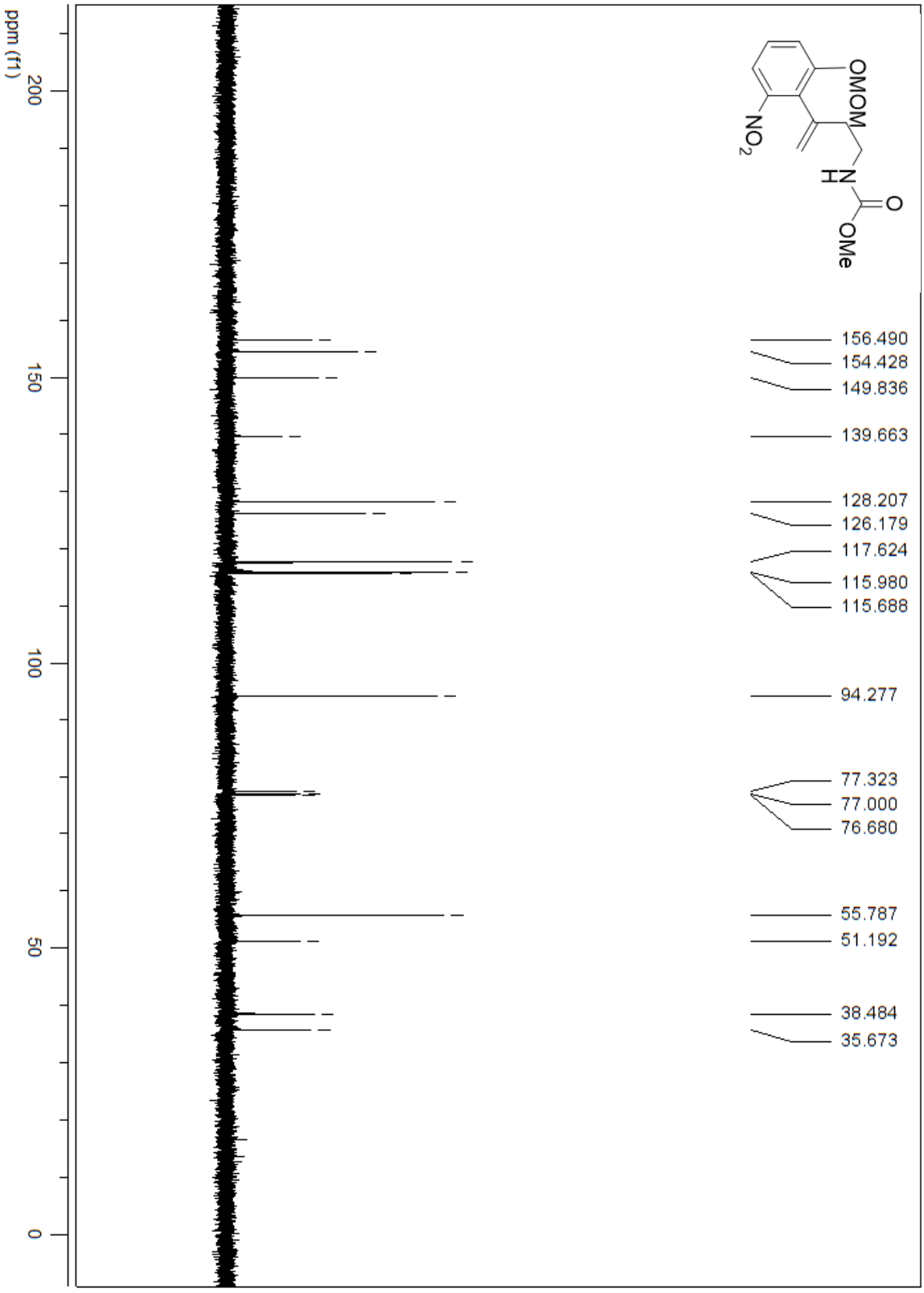

Figure 98: ^{13}C NMR of [3-(2-methoxymethoxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester **(68)**

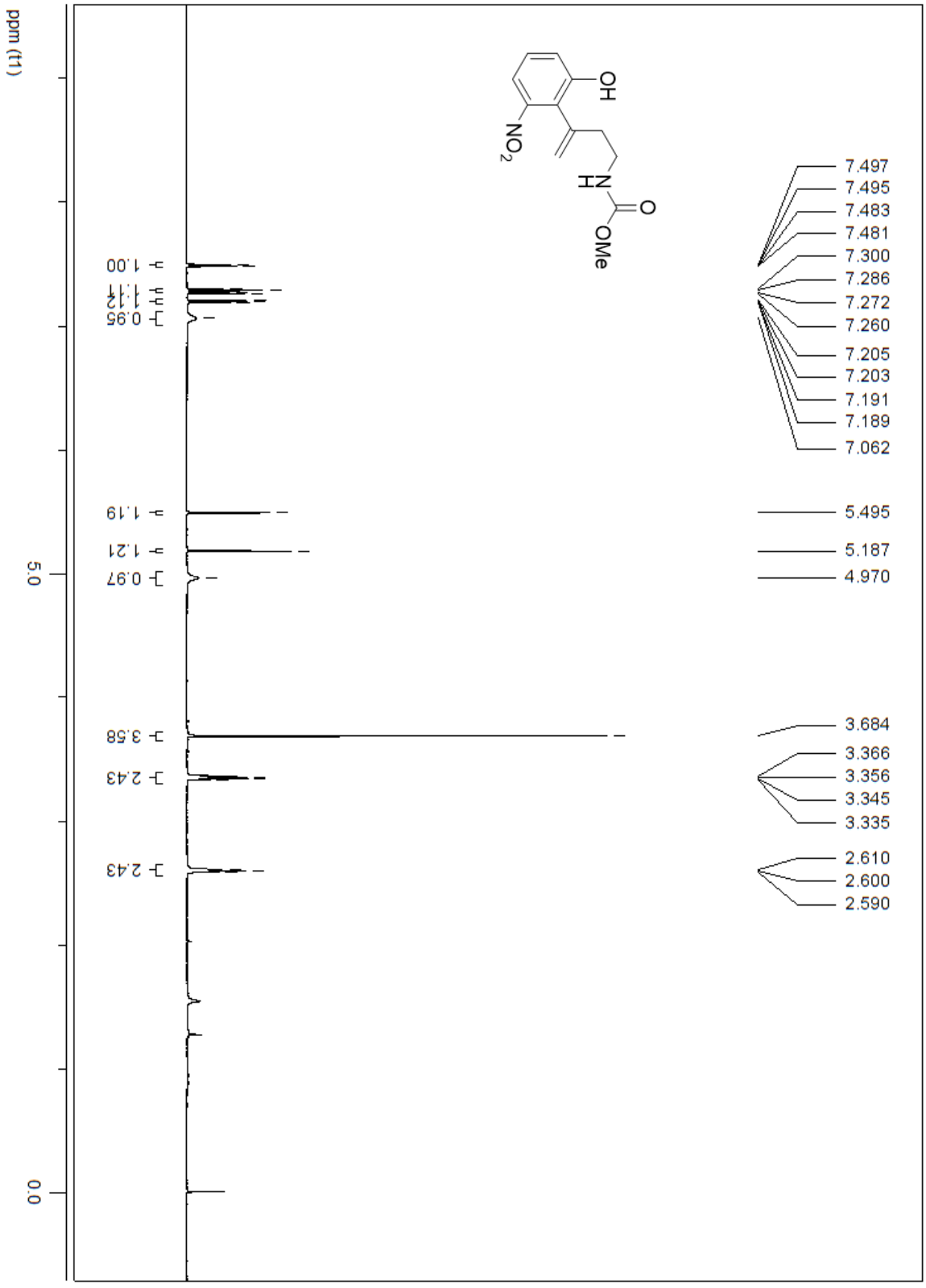

Figure 99: ^{1}H NMR (65 ^{o}C) of [3-(2-hydroxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester **(54)**

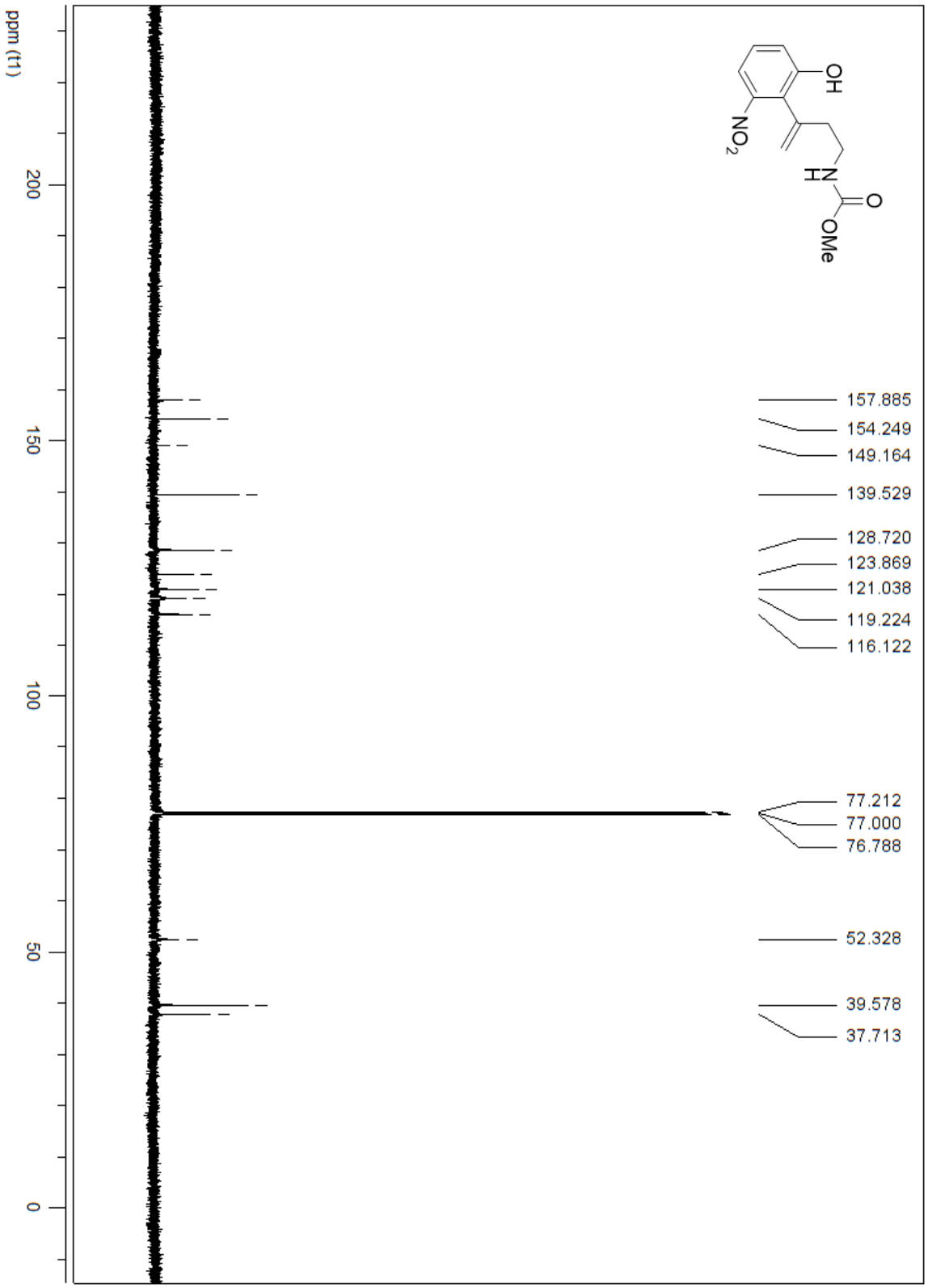

Figure 100: ^{13}C NMR (65 ºC) of [3-(2-hydroxy-6-nitro-phenyl)-but-3-enyl]-carbamic acid methyl ester **(54)**

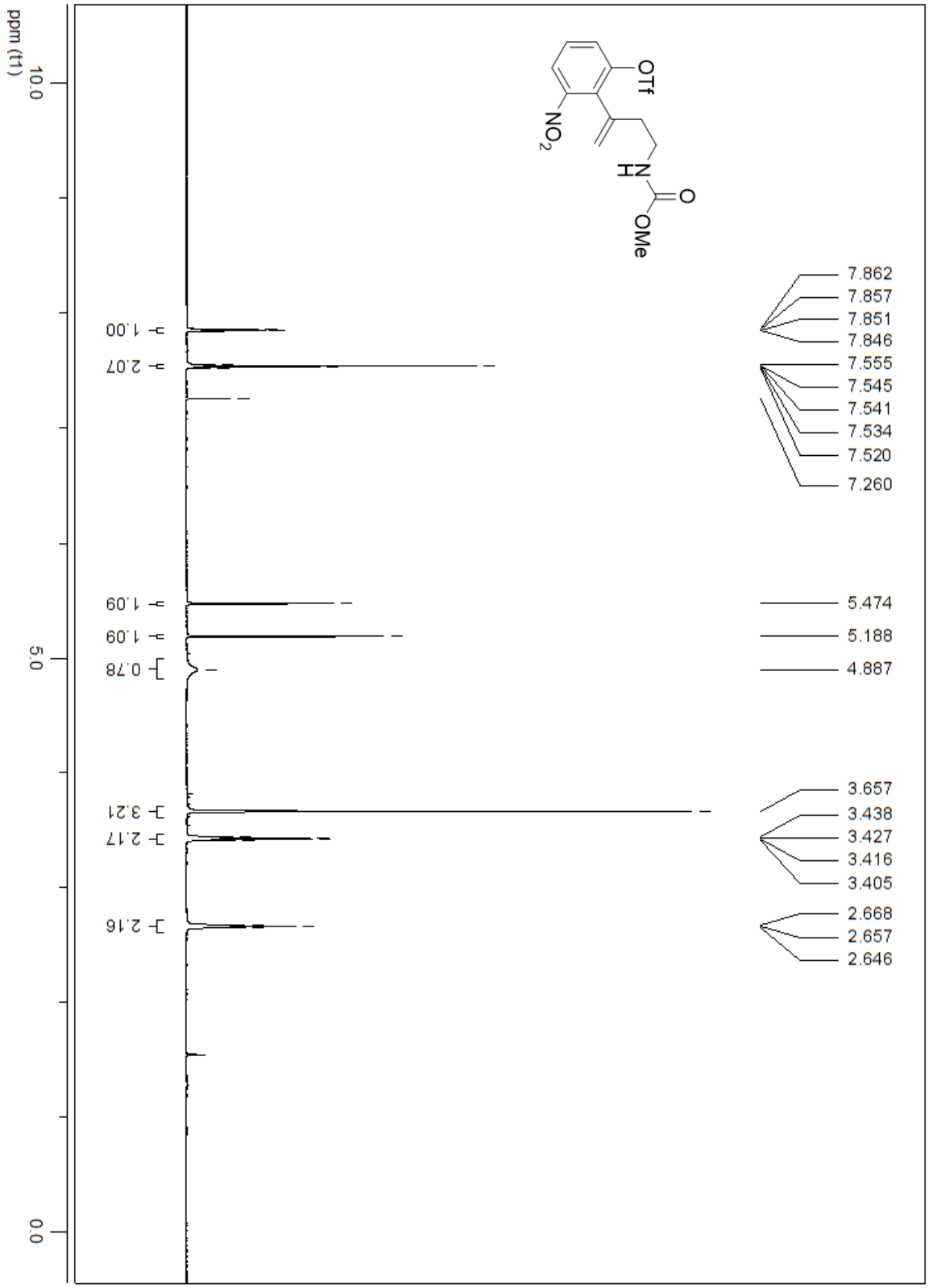

Figure 101: ^{1}H NMR (65 ^{o}C) of trifluoro-methanesulfonic acid 2-(3-methoxy-carbonylamino-1-methylene-propyl)-3-nitro-phenyl ester **(53)**

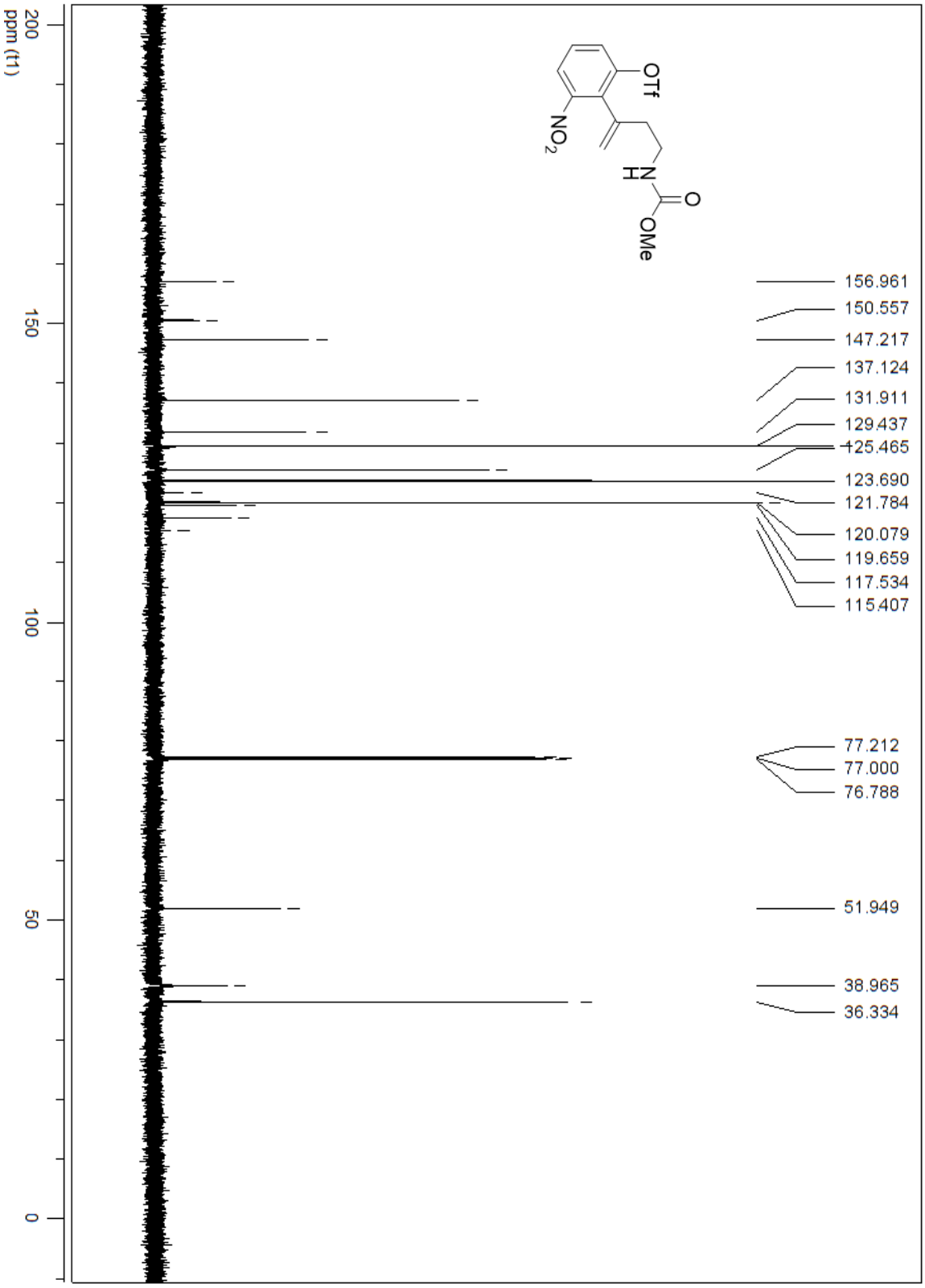

Figure 102: ^{13}C NMR (65 ^{o}C) of trifluoro-methanesulfonic acid 2-(3-methoxy-carbonylamino-1-methylene-propyl)-3-nitro-phenyl ester **(53)**

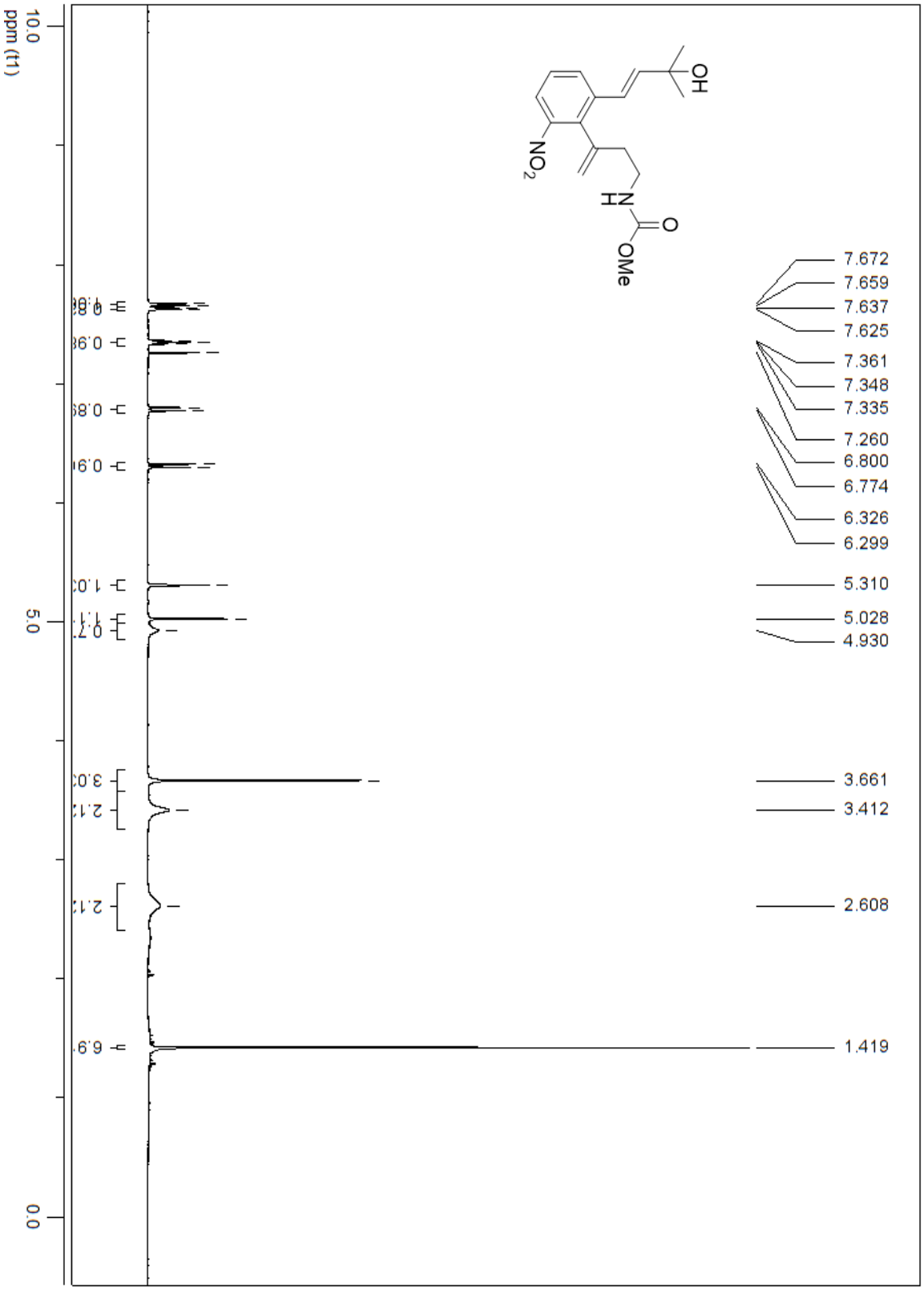

Figure 103: ^{1}H NMR (65 ^{o}C) of {3-[2-(3-hydroxy-3-methyl-but-1-enyl)-6-nitro-phenyl]-but-3-enyl}-carbamic acid methyl ester **(69)**

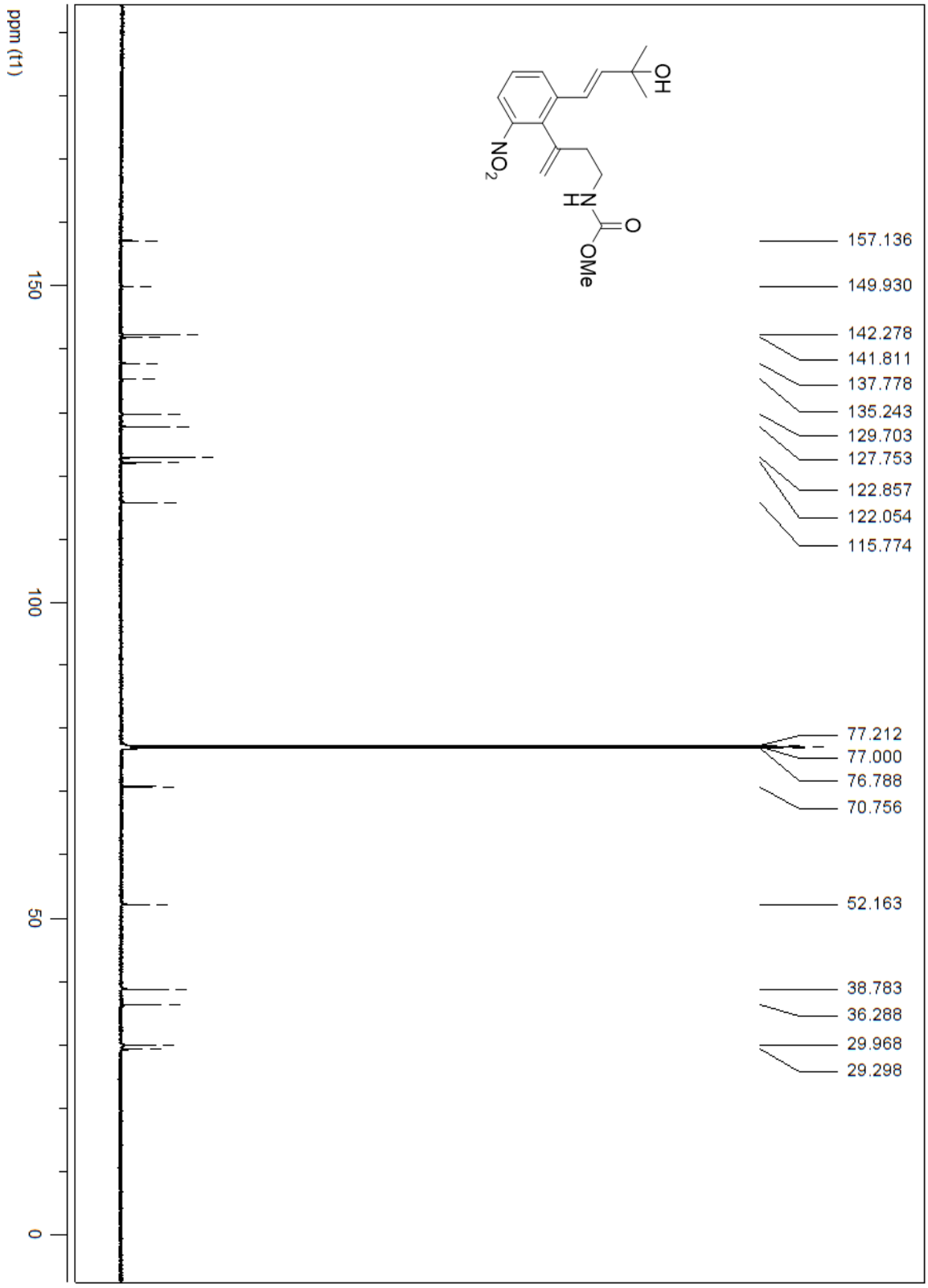

Figure 104: ^{13}C NMR of {3-[2-(3-hydroxy-3-methyl-but-1-enyl)-6-nitro-phenyl]-but- 3-enyl}-carbamic acid methyl ester **(69)**

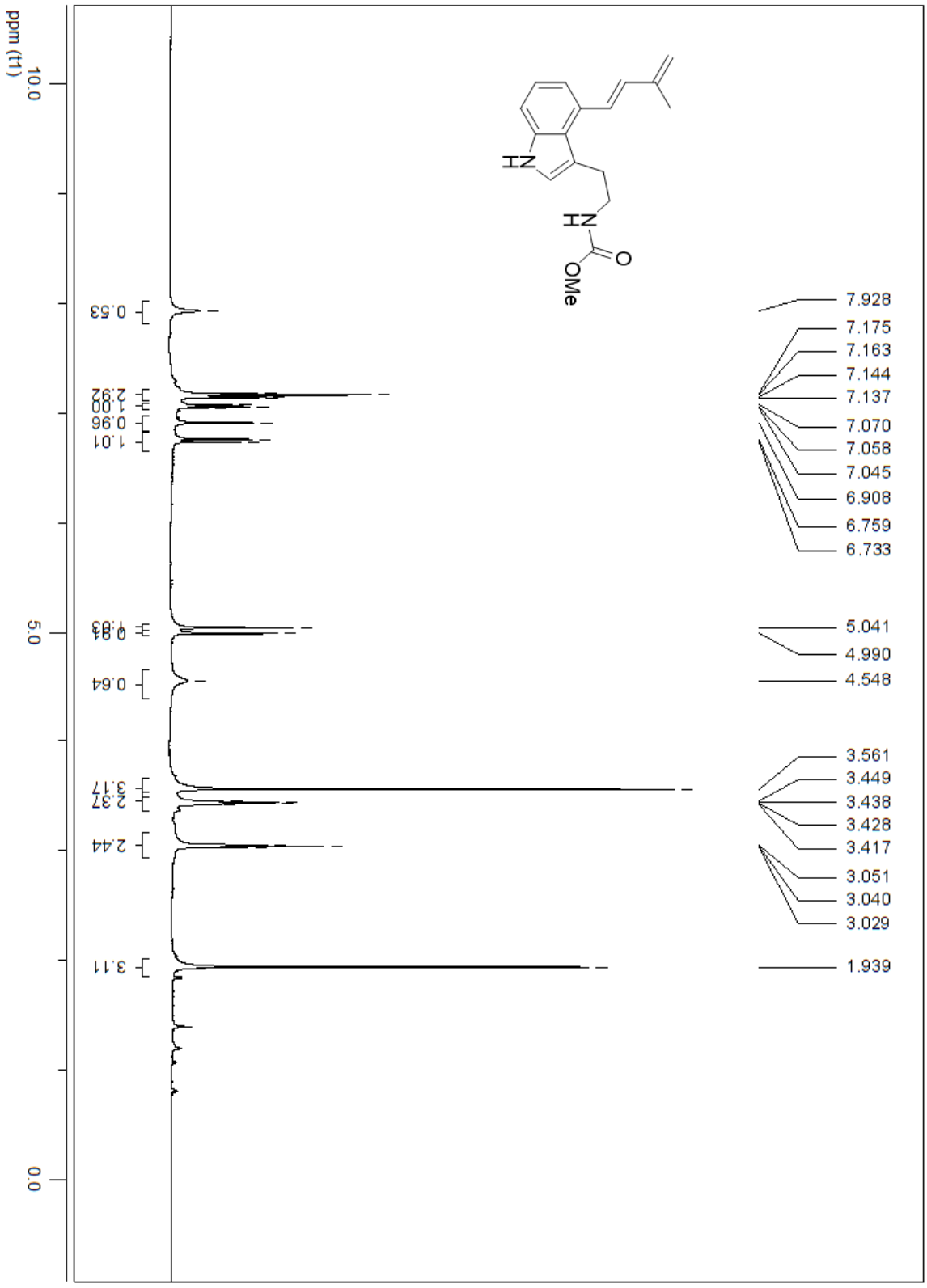

Figure 105: ^{1}H NMR (65 ^{o}C) of {2-[4-(3-methyl-buta-1,3-dienyl)-1H-indol-3-yl]-ethyl}-carbamic acid methyl ester **(70)**

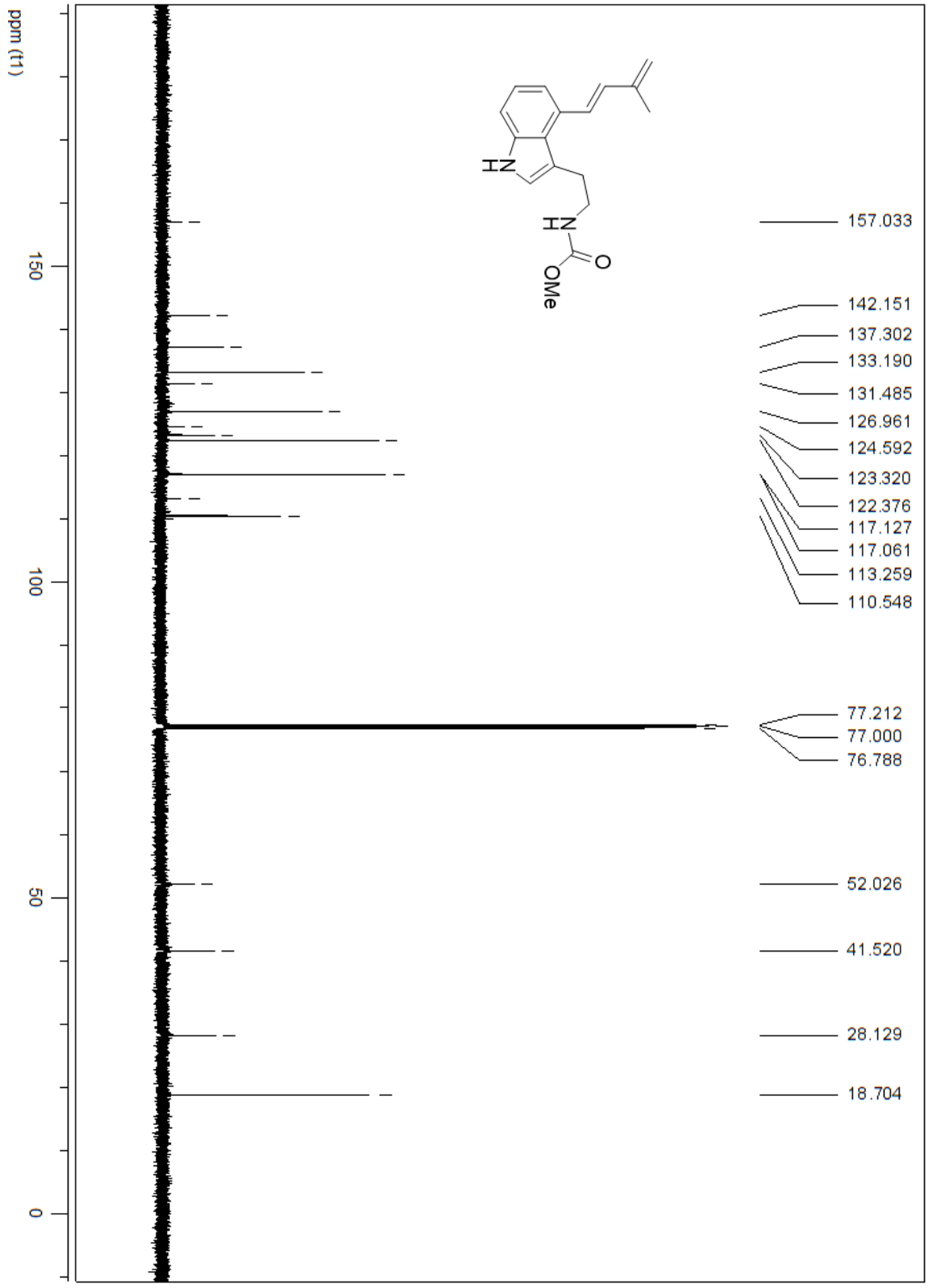

Figure 106: ^{13}C NMR of {2-[4-(3-methyl-buta-1,3-dienyl)-1H-indol-3-yl]-ethyl}-carbamic acid methyl ester **(70)**

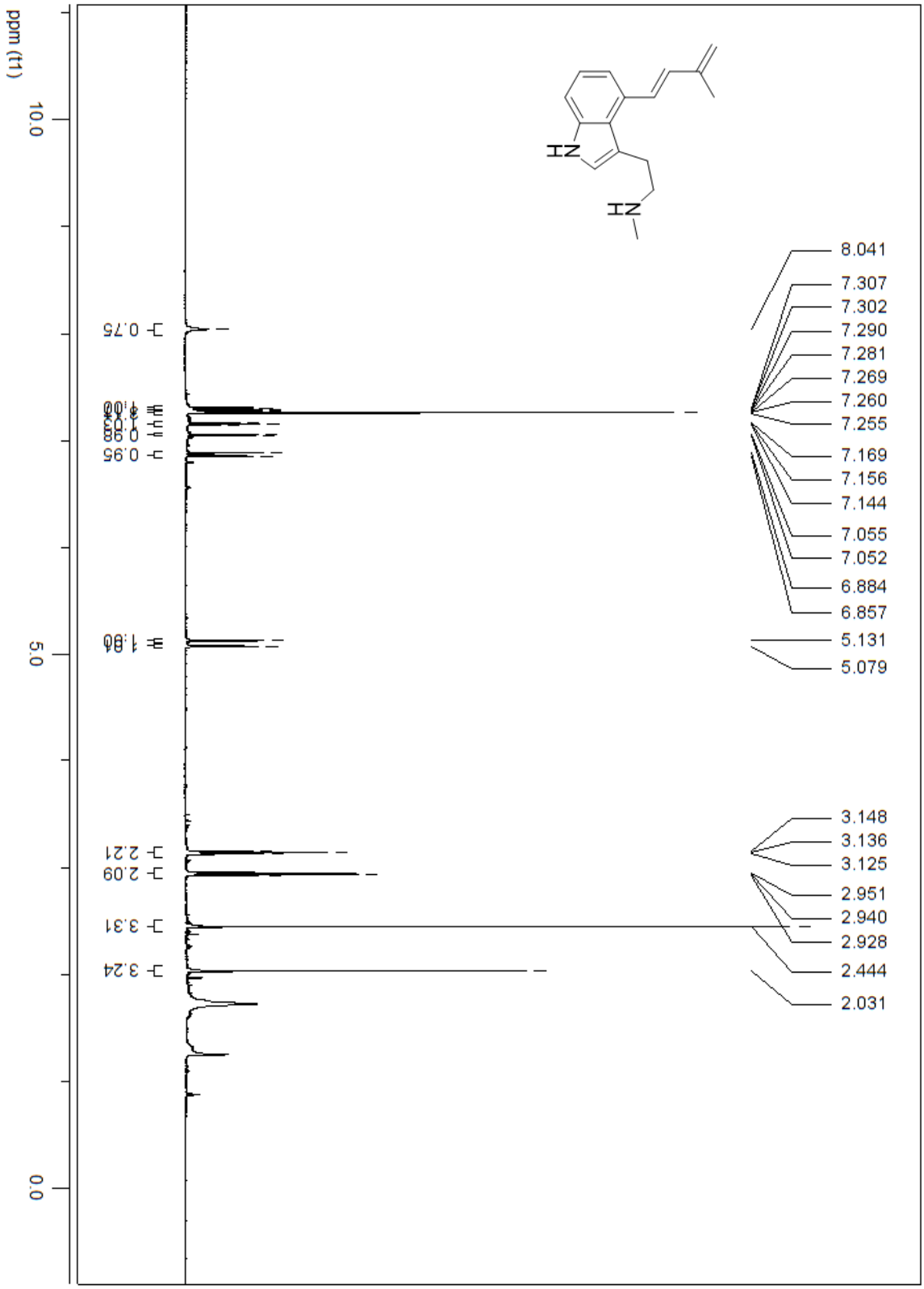

Figure 107: ^{1}H NMR of methyl-{2-[4-(3-methyl-buta-1,3-dienyl)-1H-indol-3-yl]-ethyl}-amine **(dehydrated ergotryptamine)**

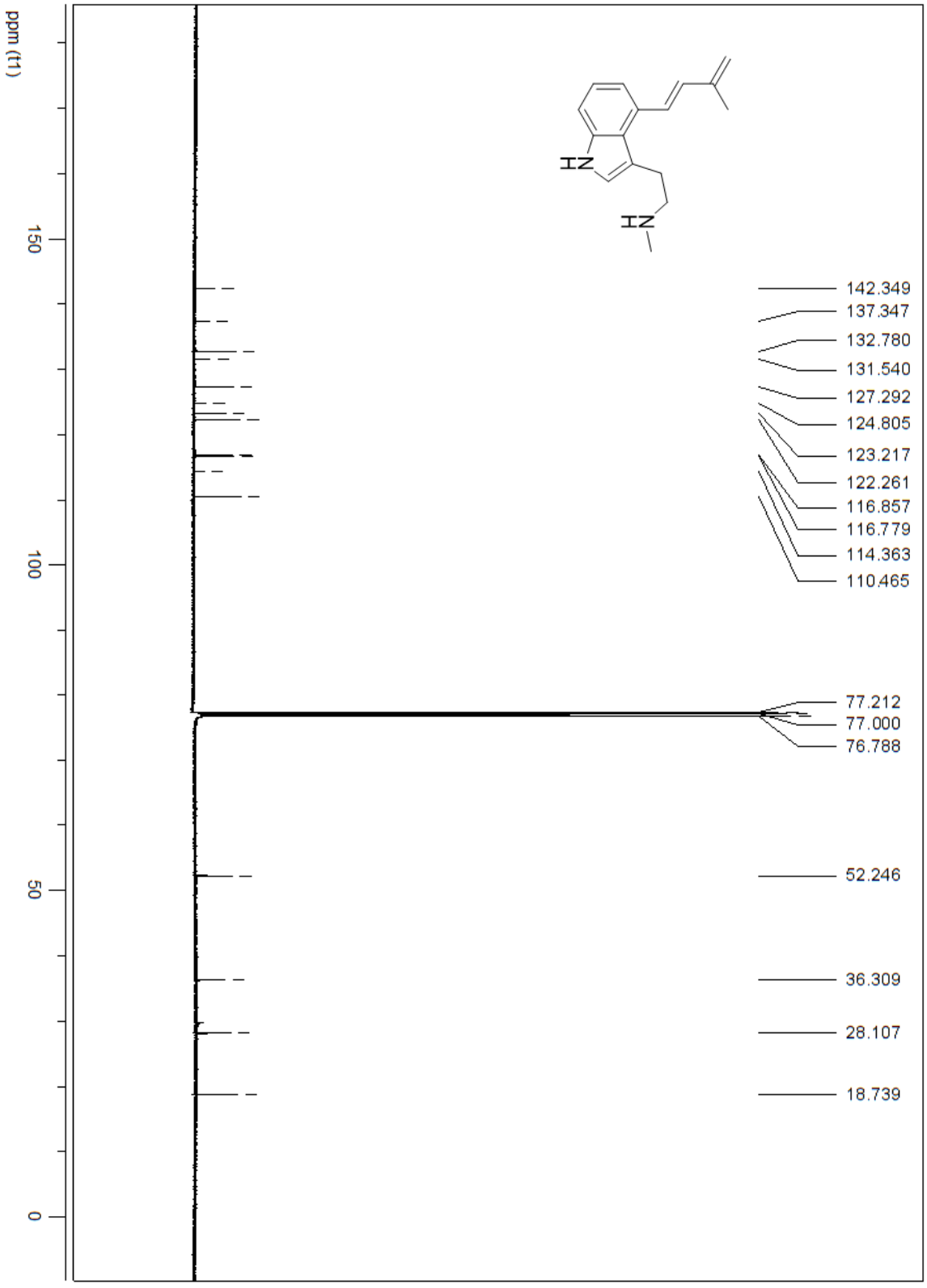

Figure 108: ^{13}C NMR of methyl-{2-[4-(3-methyl-buta-1,3-dienyl)-1H-indol-3-yl]-ethyl}-amine **(dehydrated ergotryptamine)**

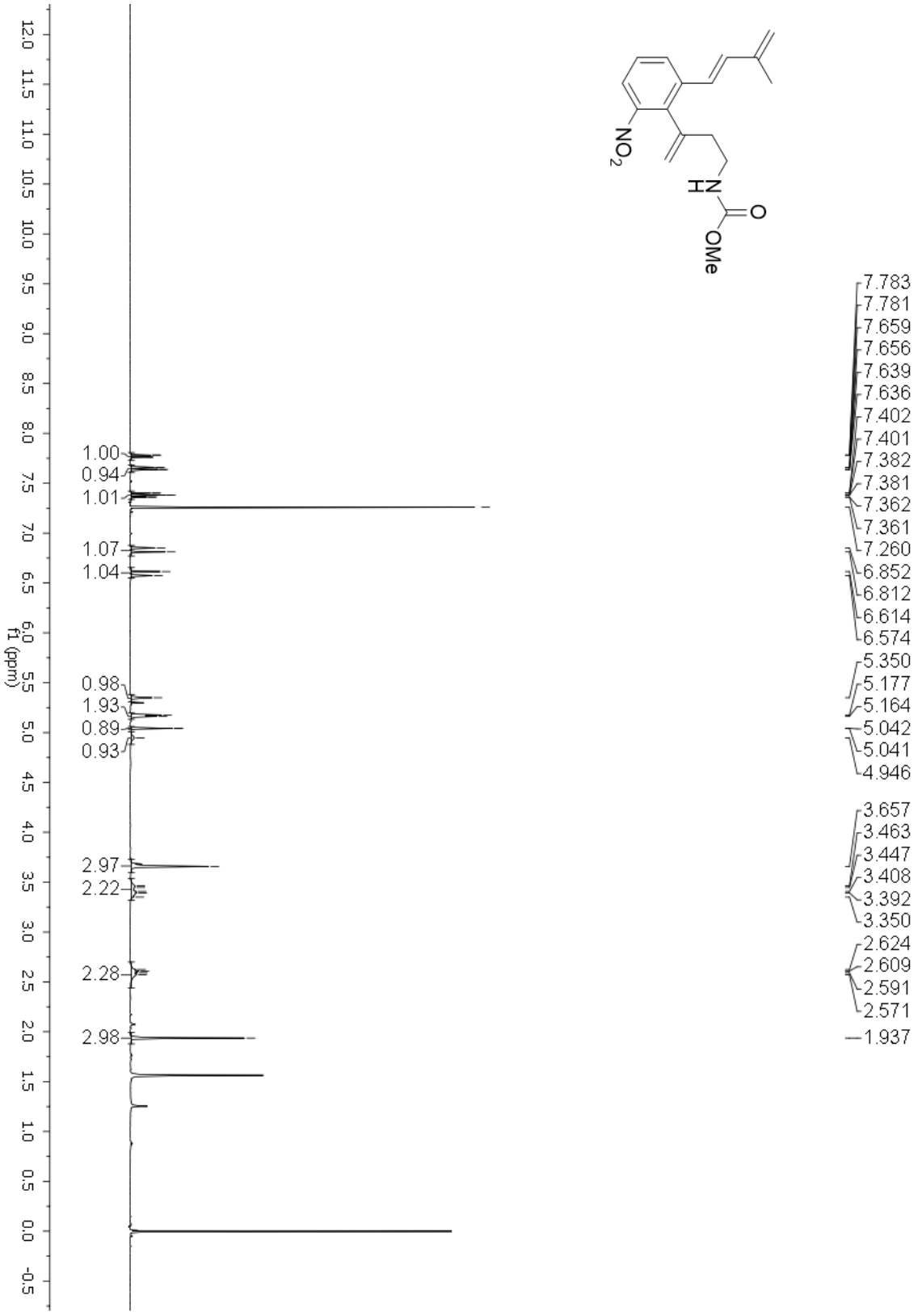

Figure 109: ^{1}H NMR of {3-[2-(3-methyl-buta-1,3-dienyl)-6-nitro-phenyl]-but-3-enyl}-carbamic acid methyl ester **(71)**

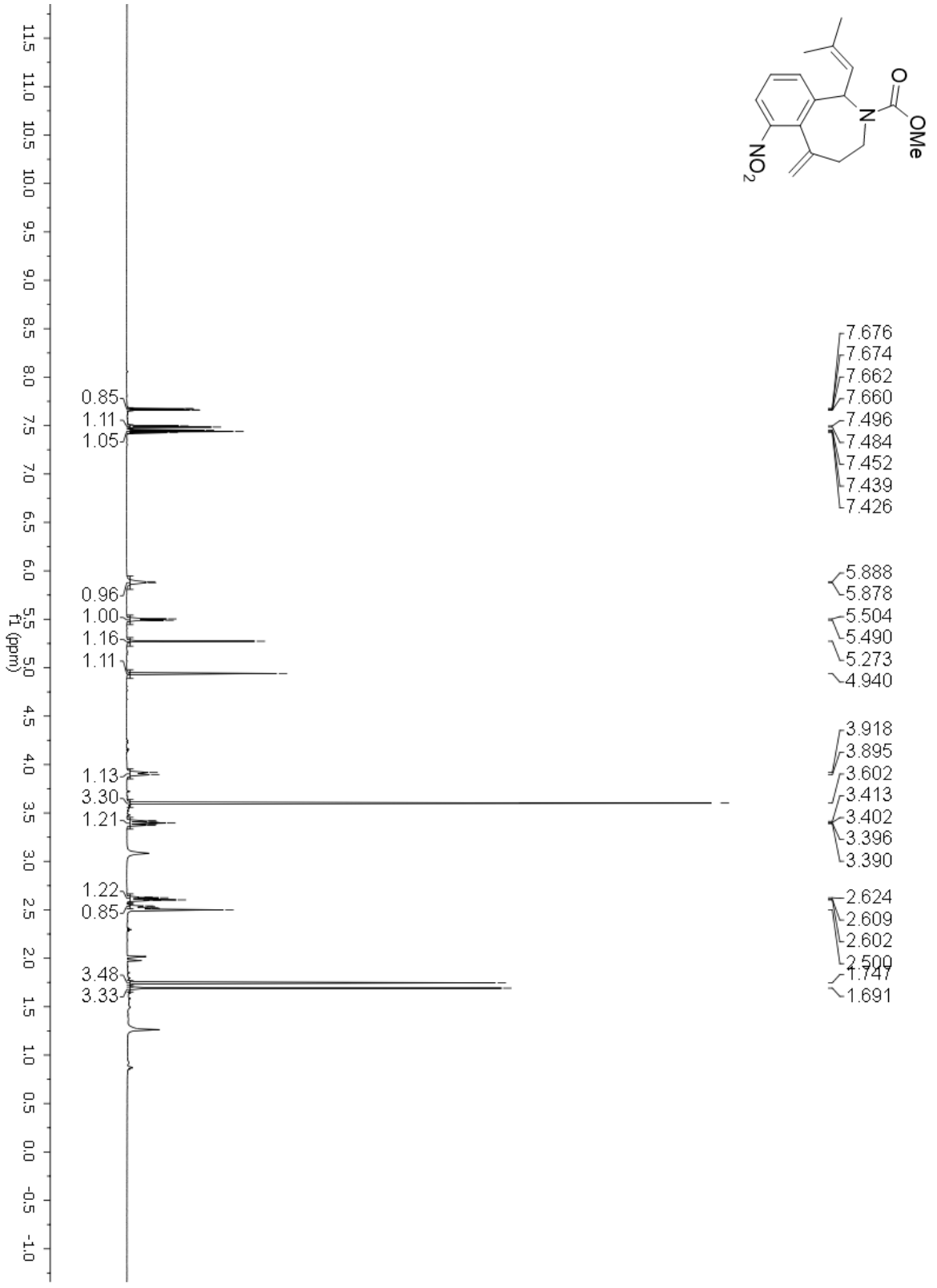

Figure 110: ^{1}H NMR (75 ºC) of 5-methylene-1-(2-methyl-propenyl)-6-nitro-1,3,4,5-tetrahydro-benzo[c]azepine-2-carboxylic acid methyl ester **(72)**

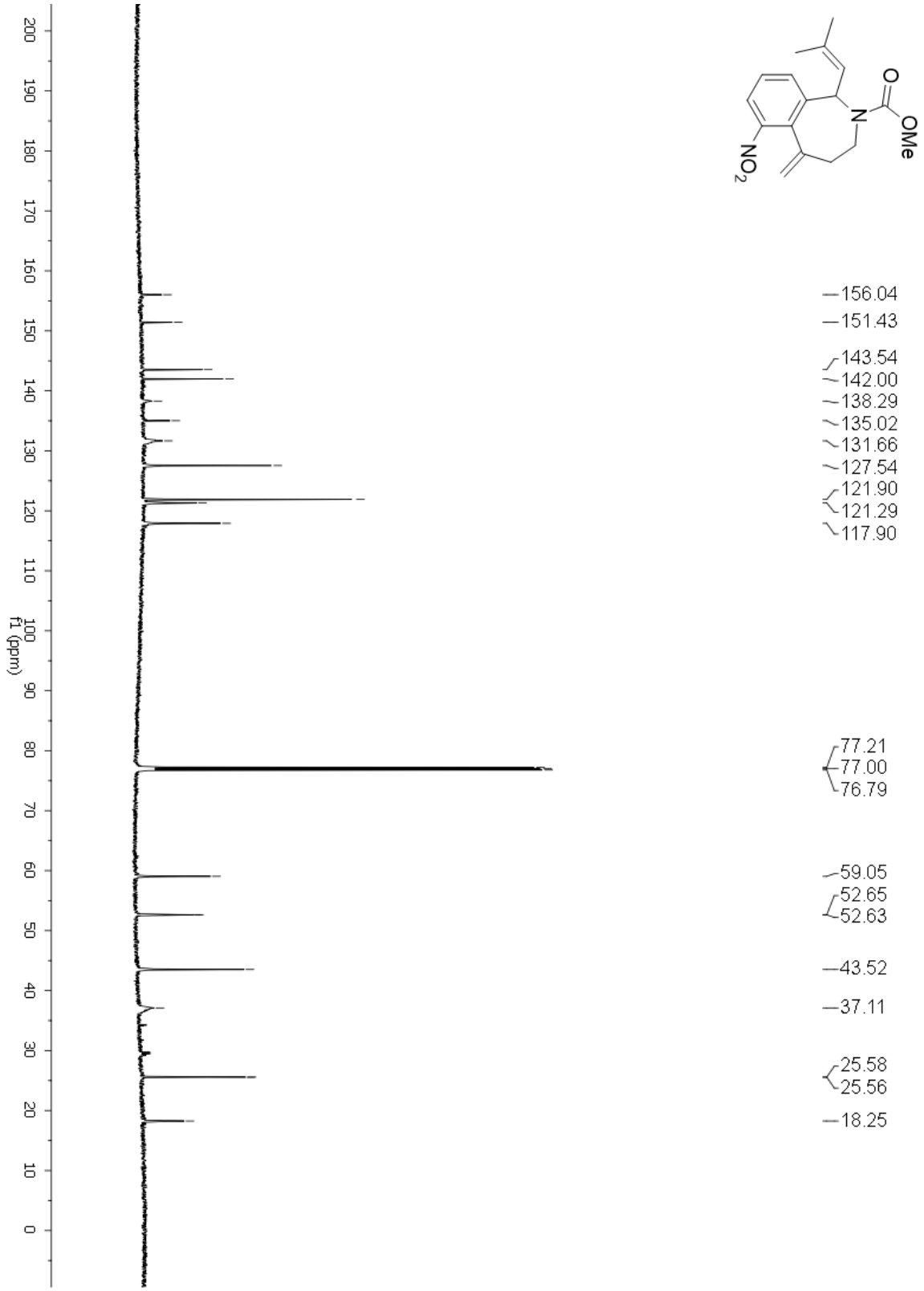

Figure 111: ^{13}C NMR (65 ºC) of 5-methylene-1-(2-methyl-propenyl)-6-nitro-1,3,4,5-tetrahydro-benzo[c]azepine-2-carboxylic acid methyl ester **(72)**

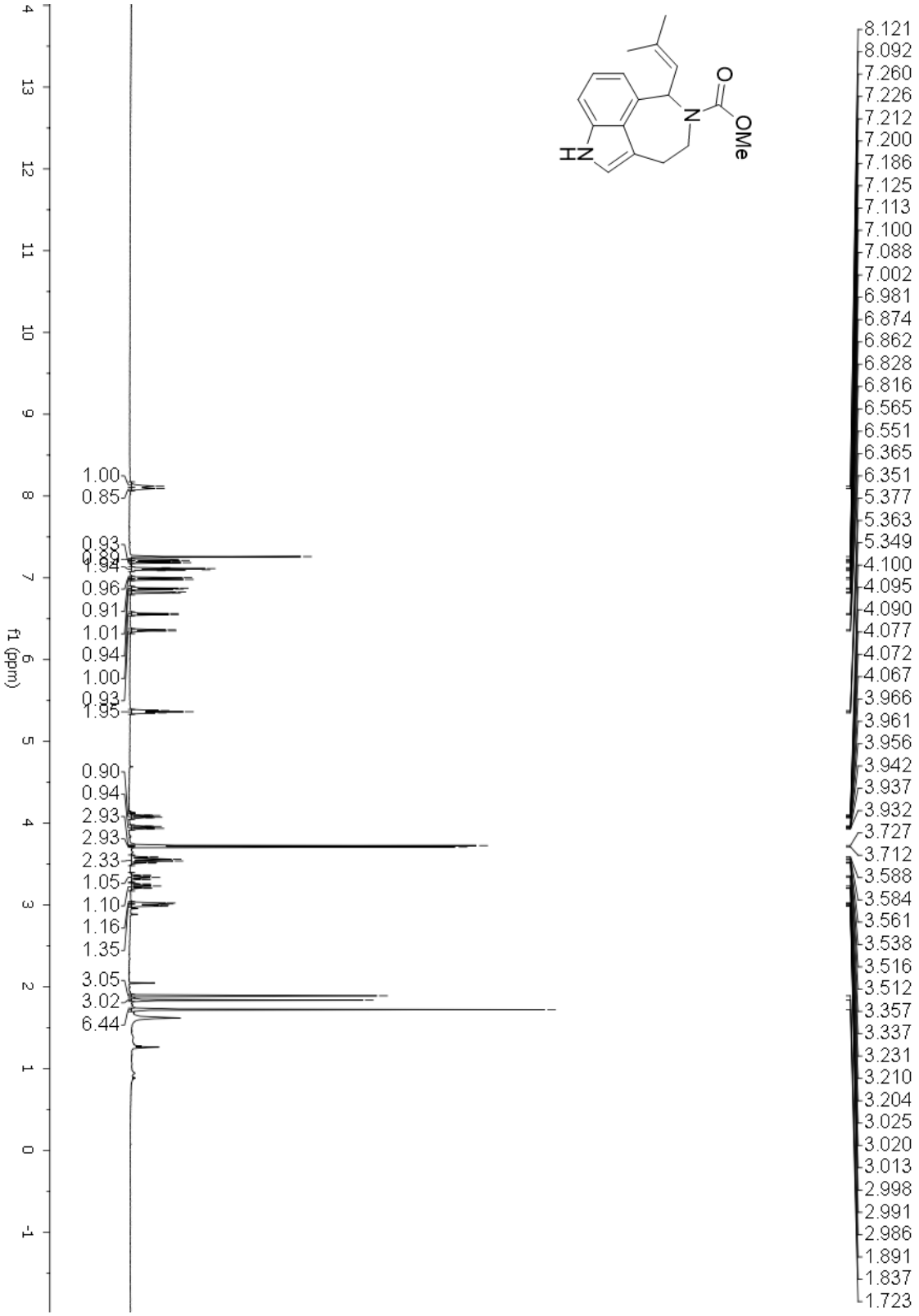

Figure 112: ^{1}H NMR of 6-(2-methyl-propenyl)-3,4-dihydro-1H,6H-azepino[5,4,3-cd]indole-5-carboxylic acid methyl ester **(73)**

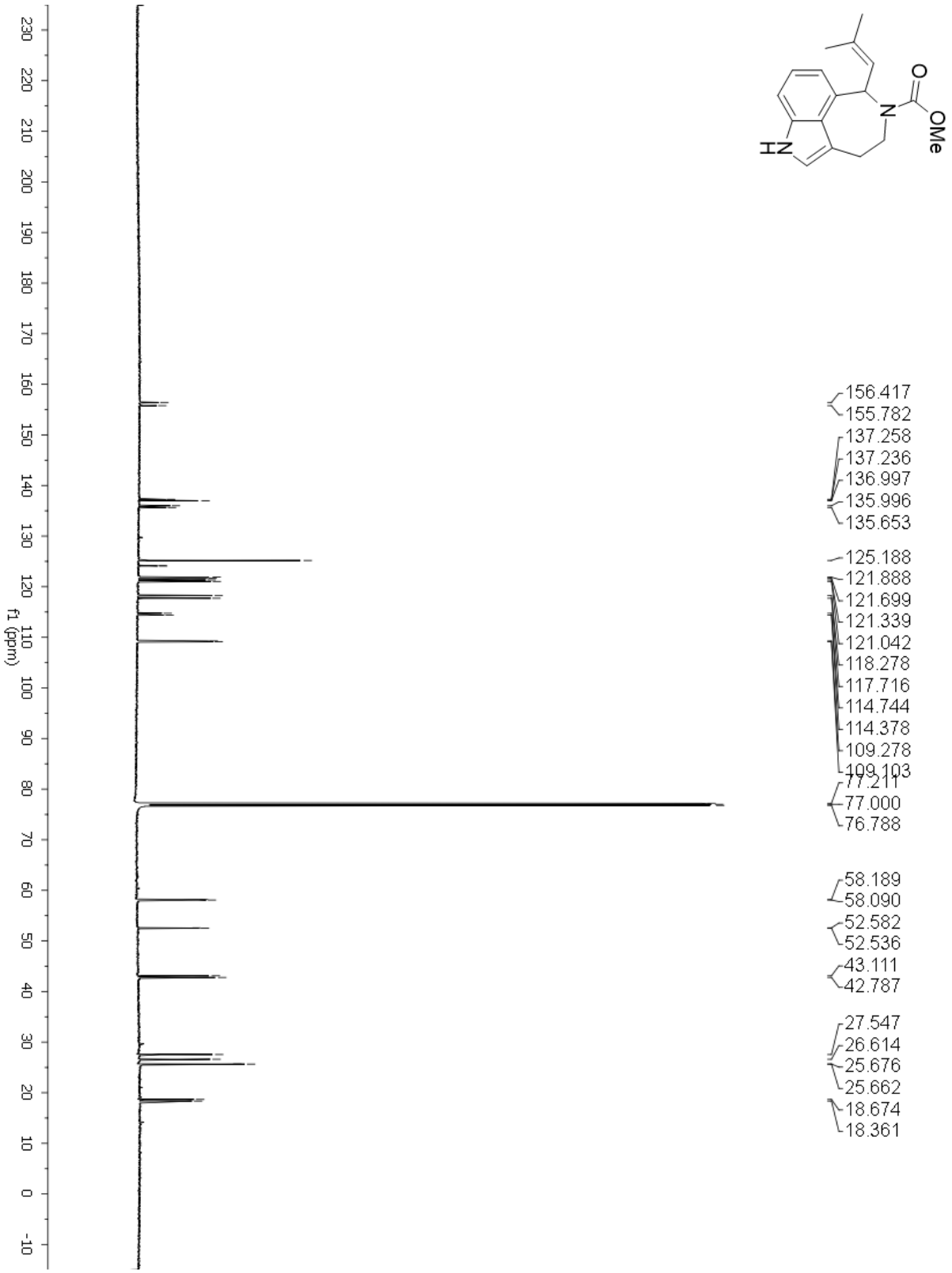

Figure 113: ^{13}C NMR of 6-(2-methyl-propenyl)-3,4-dihydro-1H,6H-azepino[5,4,3-cd]indole-5-carboxylic acid methyl ester **(73)**

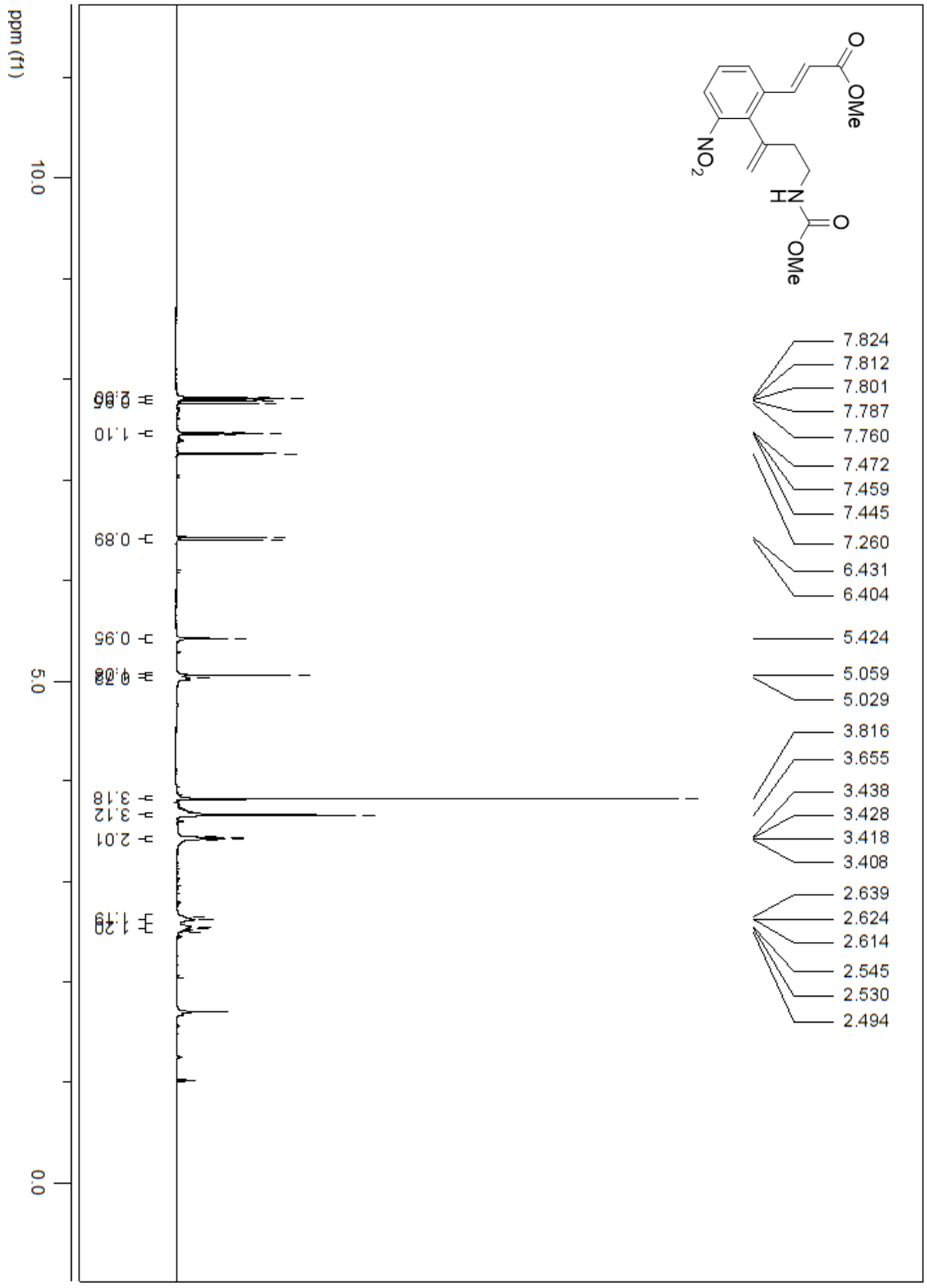

Figure 114: ^{1}H NMR of 3-[2-(3-methoxycarbonylamino-1-methylene-propyl)-3-nitro-phenyl]-acrylic acid methyl ester **(74)**

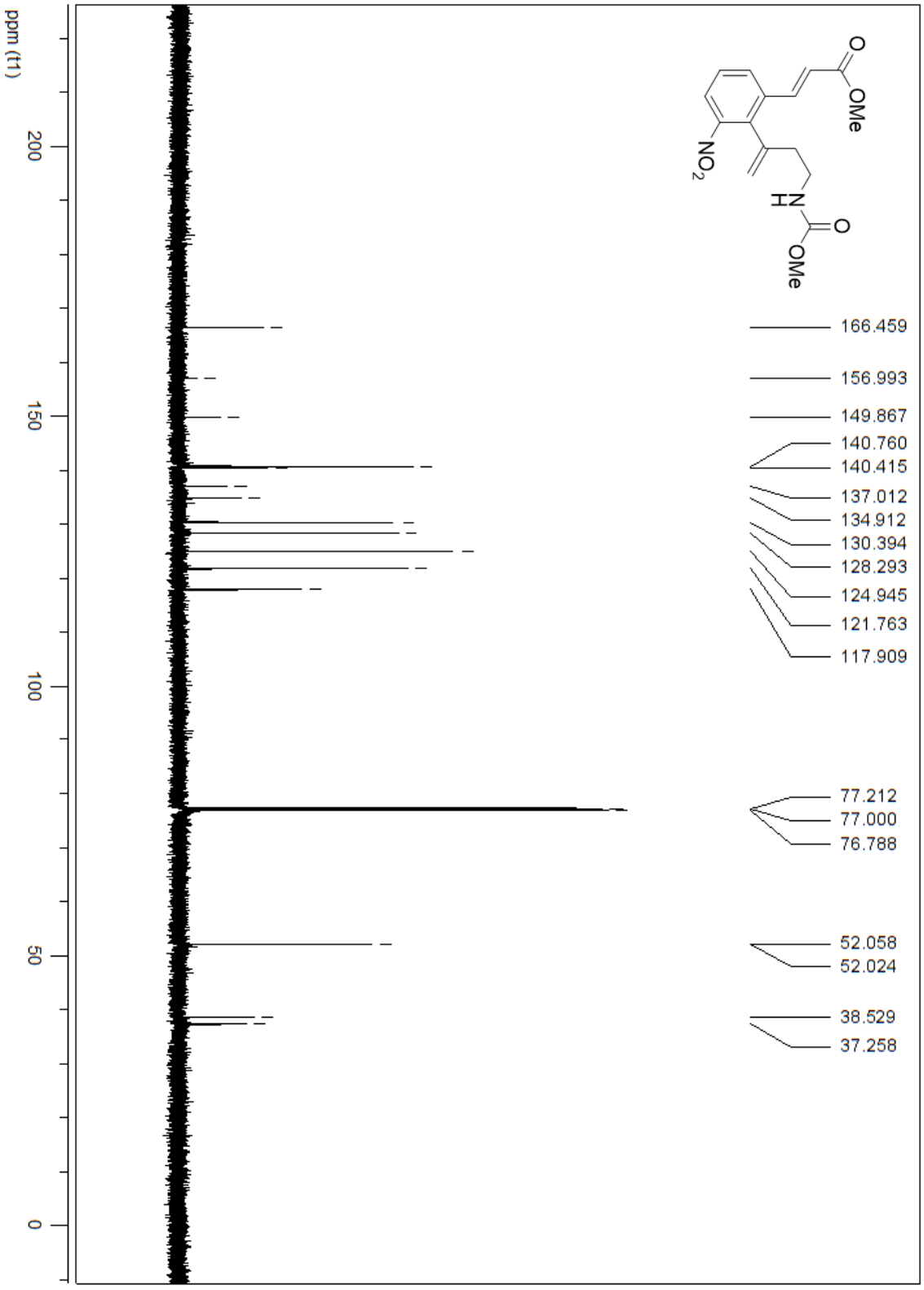

Figure 115: ^{13}C NMR of 3-[2-(3-methoxycarbonylamino-1-methylene-propyl)-3-nitro-phenyl]-acrylic acid methyl ester **(74)**

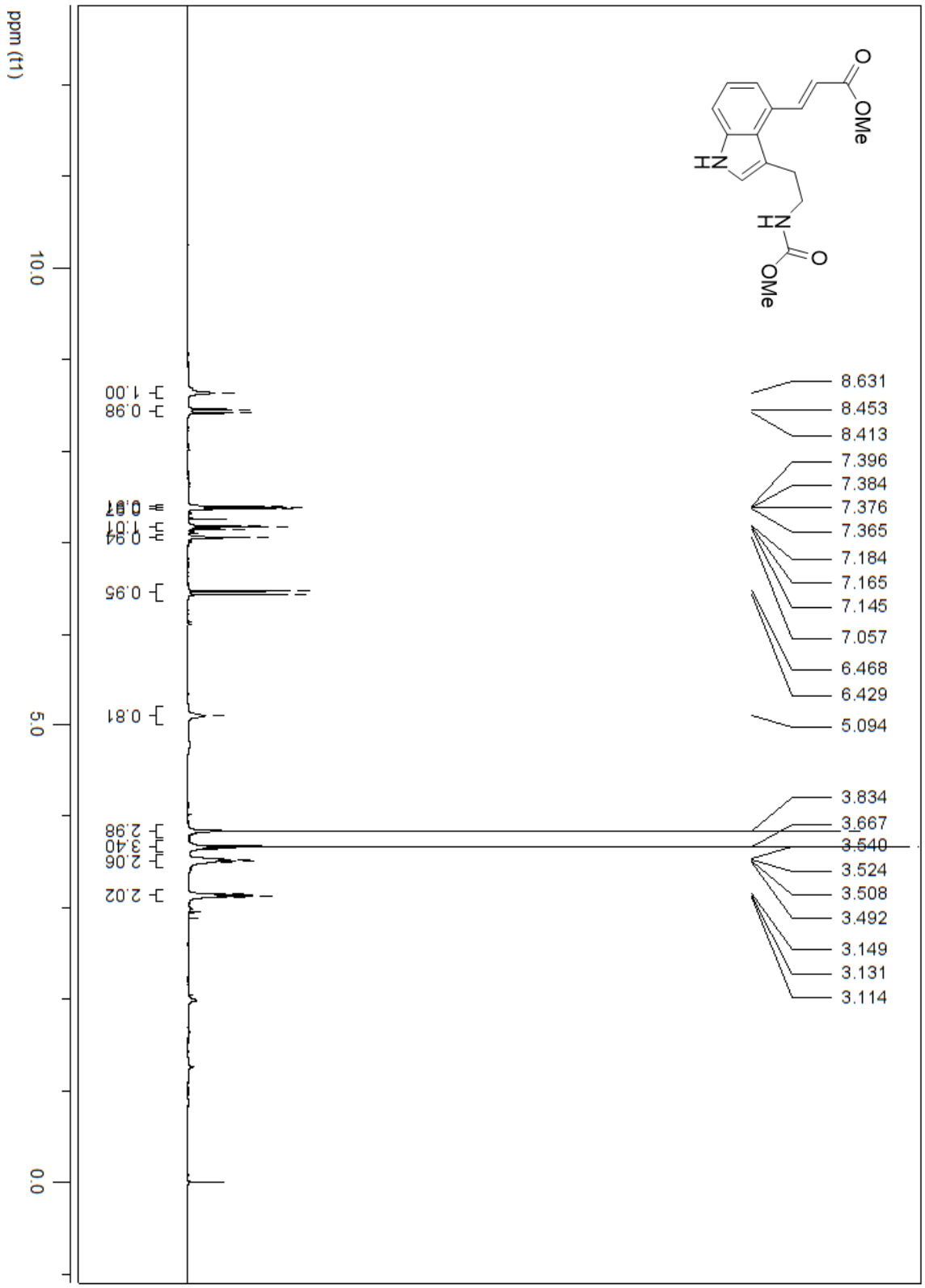

Figure 116: ^{1}H NMR of 3-[3-(2-methoxycarbonylamino-ethyl)-1H-indol-4-yl]-acrylic acid methyl ester **(75)**

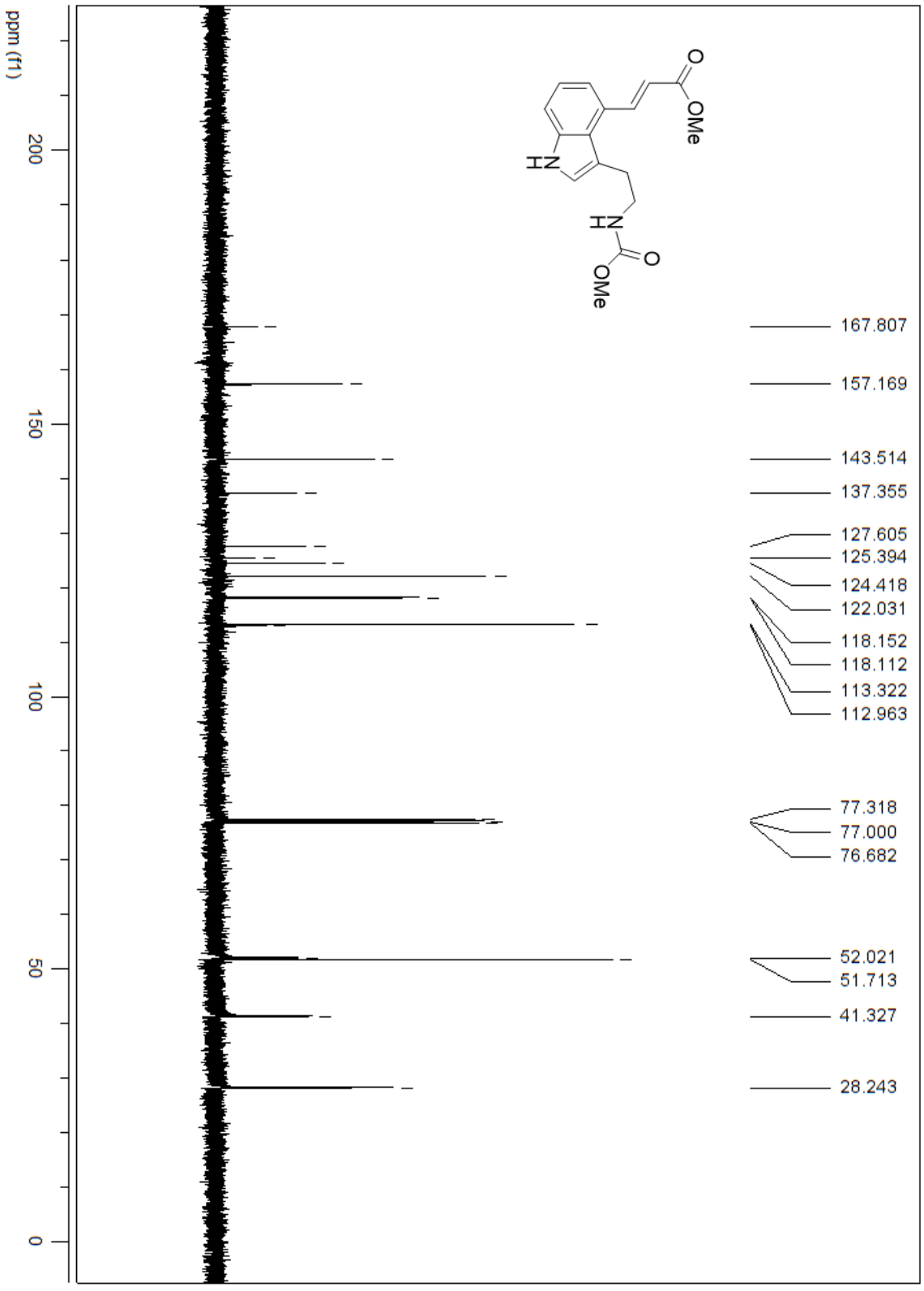

Figure 117: ^{13}C NMR of 3-[3-(2-methoxycarbonylamino-ethyl)-1H-indol-4-yl]-acrylic acid methyl ester **(75)**

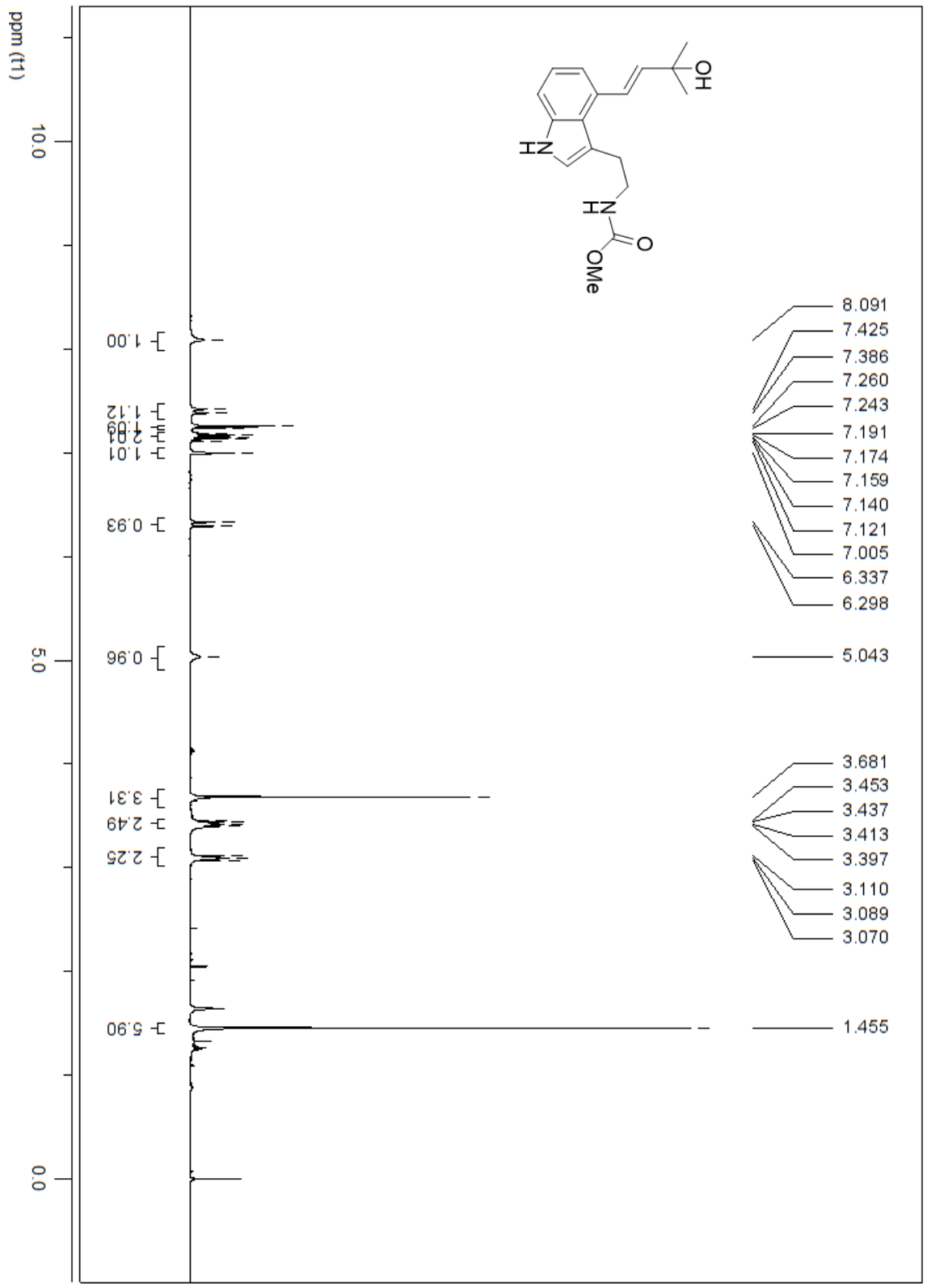

Figure 118: ^{1}H NMR of {2-[4-(3-hydroxy-3-methyl-but-1-enyl)-1H-indol-3-yl]-ethyl}-carbamic acid methyl ester **(61)**

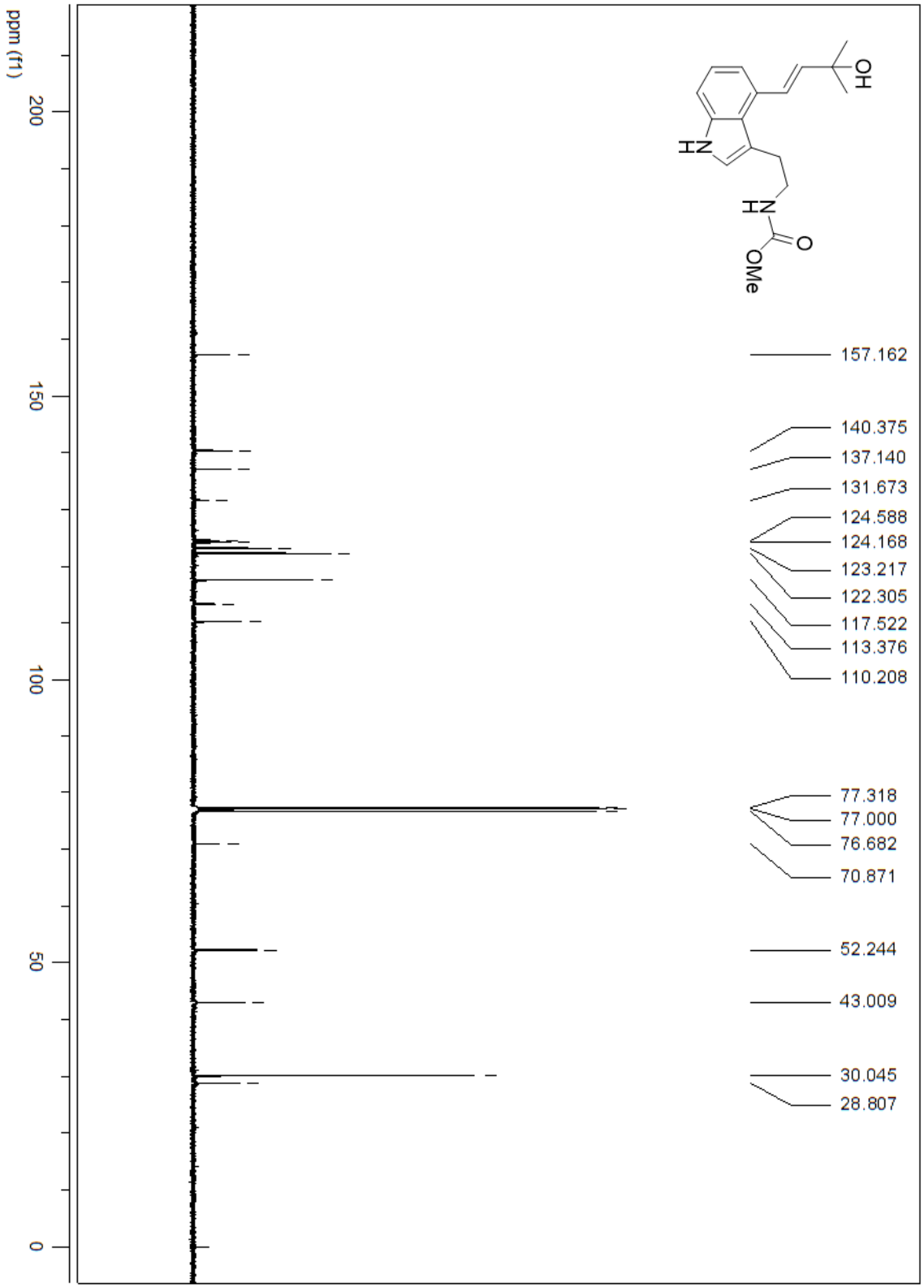

Figure 119: ^{13}C NMR of {2-[4-(3-hydroxy-3-methyl-but-1-enyl)-1H-indol-3-yl]-ethyl}-carbamic acid methyl ester **(61)**

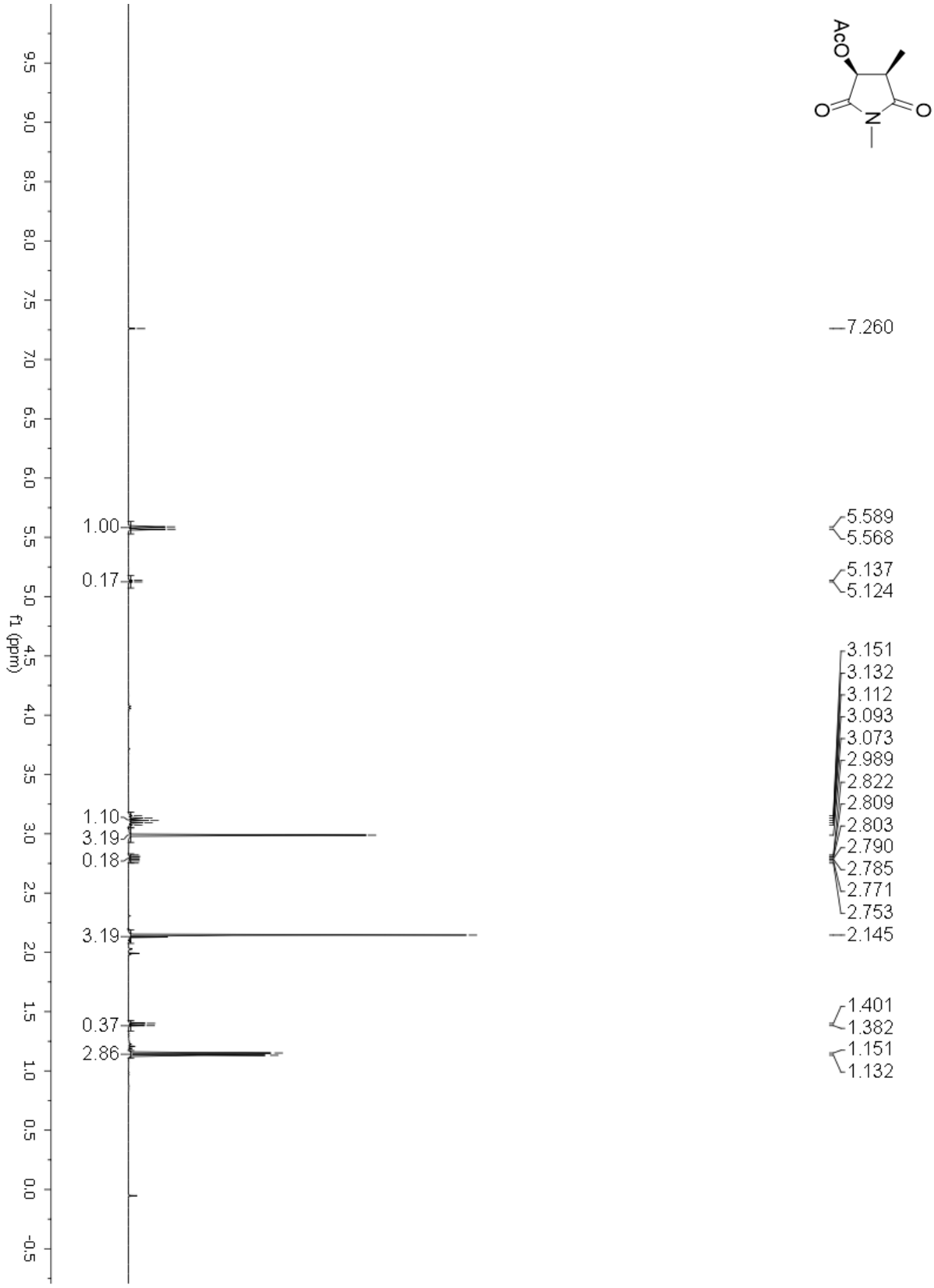

Figure 120: ^{1}H NMR of acetic acid 1,4-dimethyl-2,5-dioxo-pyrrolidin-3-yl ester **(86)**

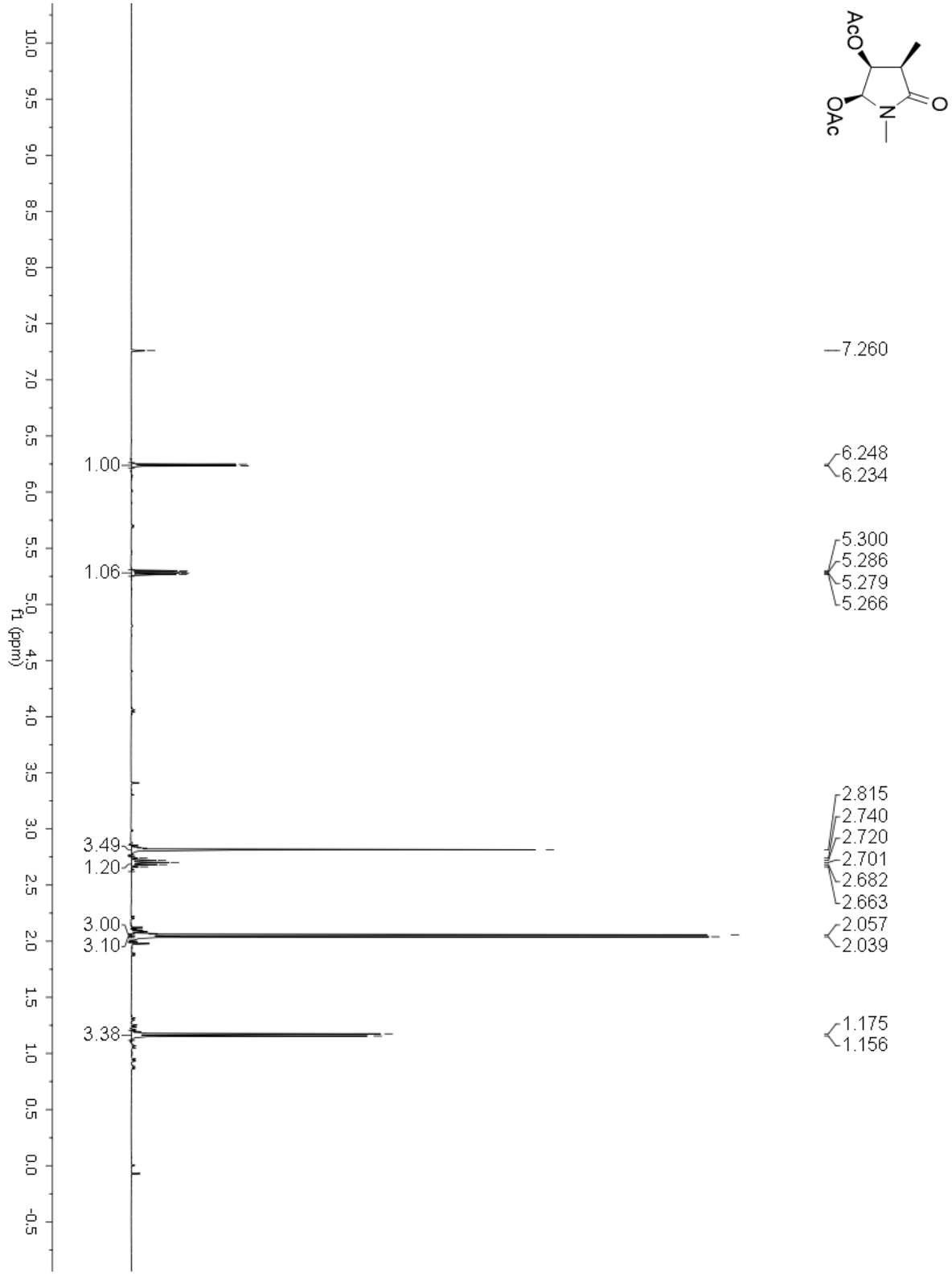

Figure 121: ^{1}H NMR of acetic acid 3-acetoxy-1,4-dimethyl-5-oxo-pyrrolidin-2-yl ester **(82)**

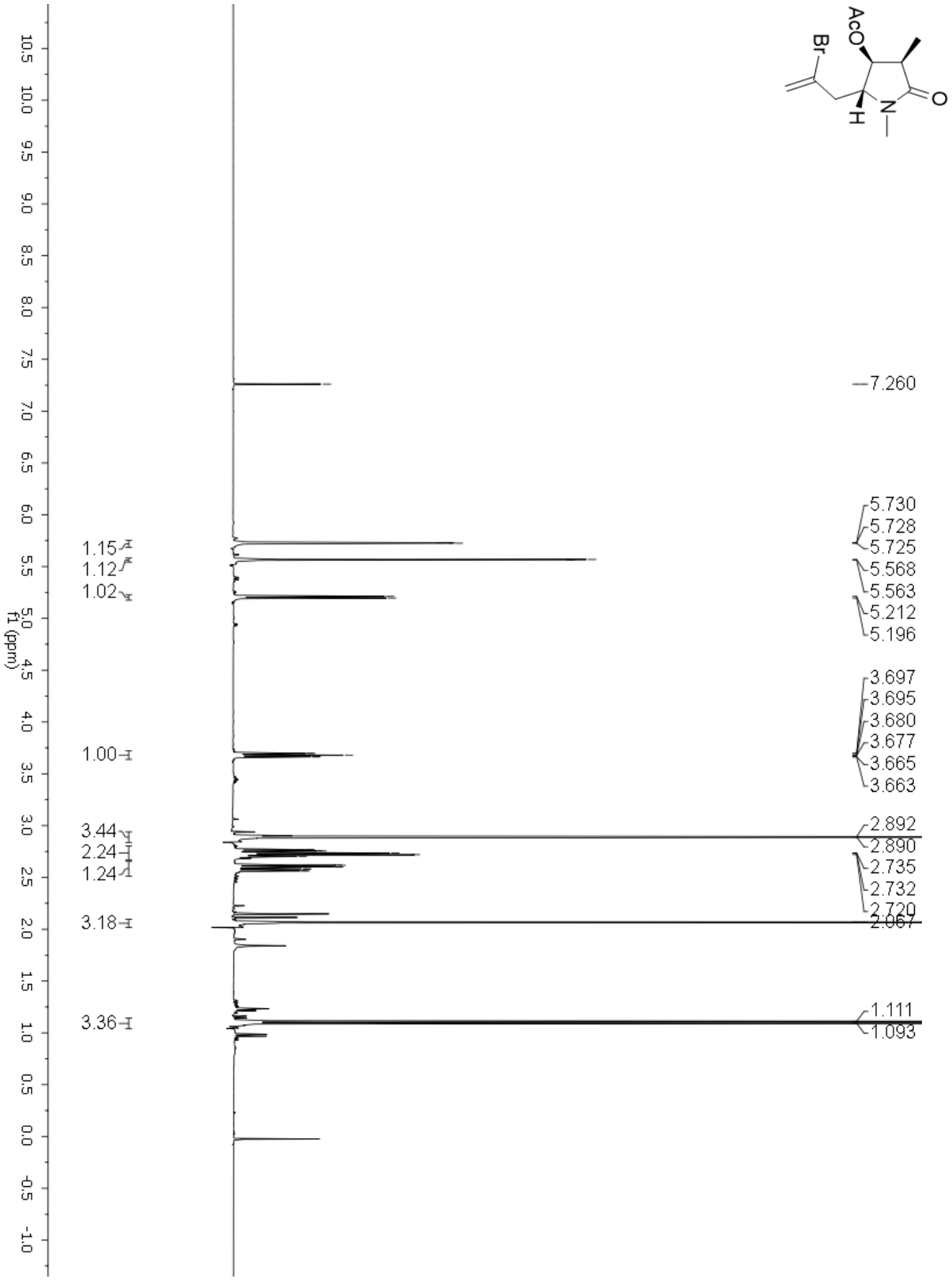

Figure 122: ^{1}H NMR of acetic acid 2-(2-bromo-allyl)-1,4-dimethyl-5-oxo-pyrrolidin-3-yl ester **(81)**

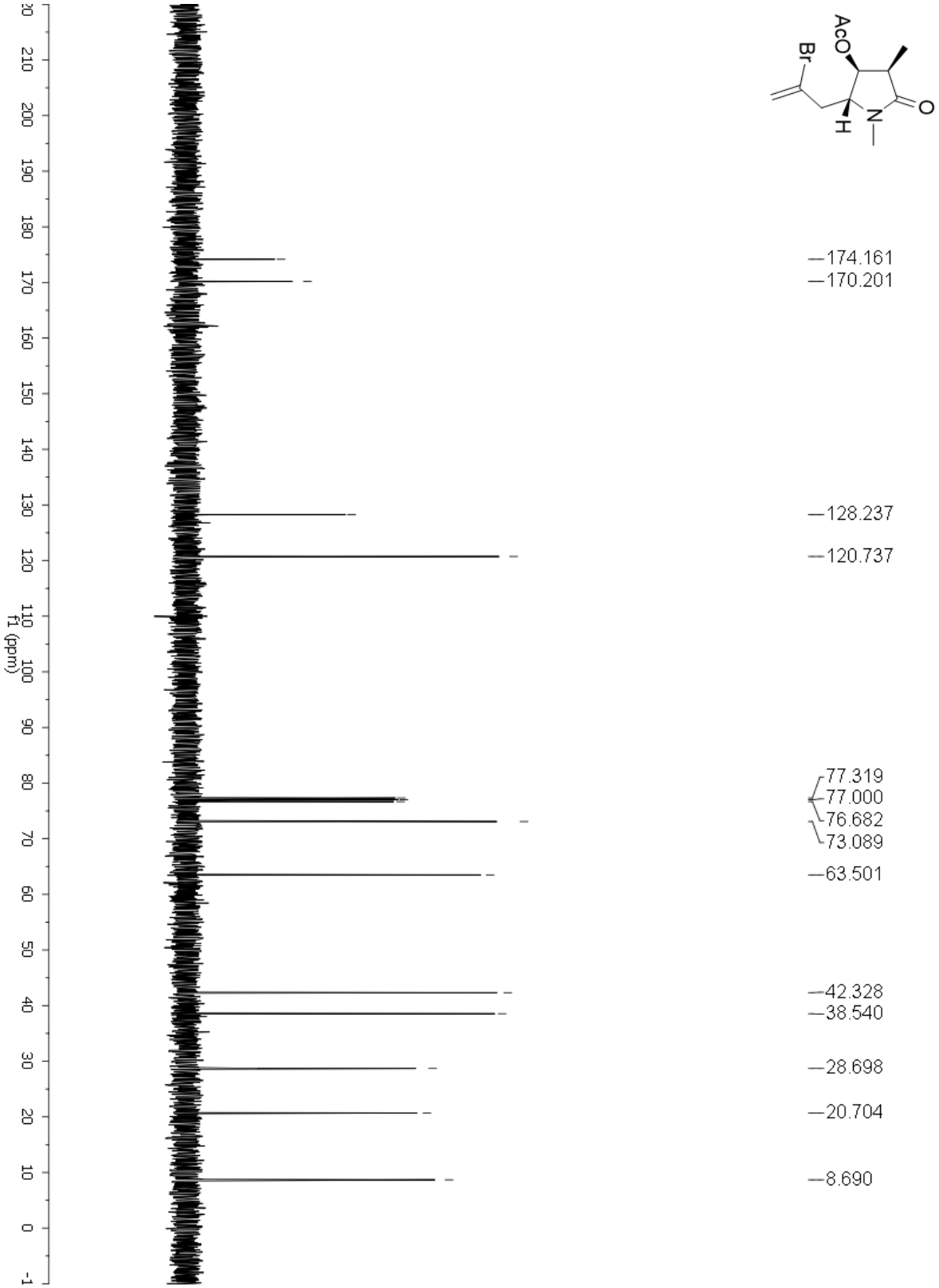

Figure 123: ^{13}C NMR of acetic acid 2-(2-bromo-allyl)-1,4-dimethyl-5-oxo-pyrrolidin-3-yl ester **(81)**

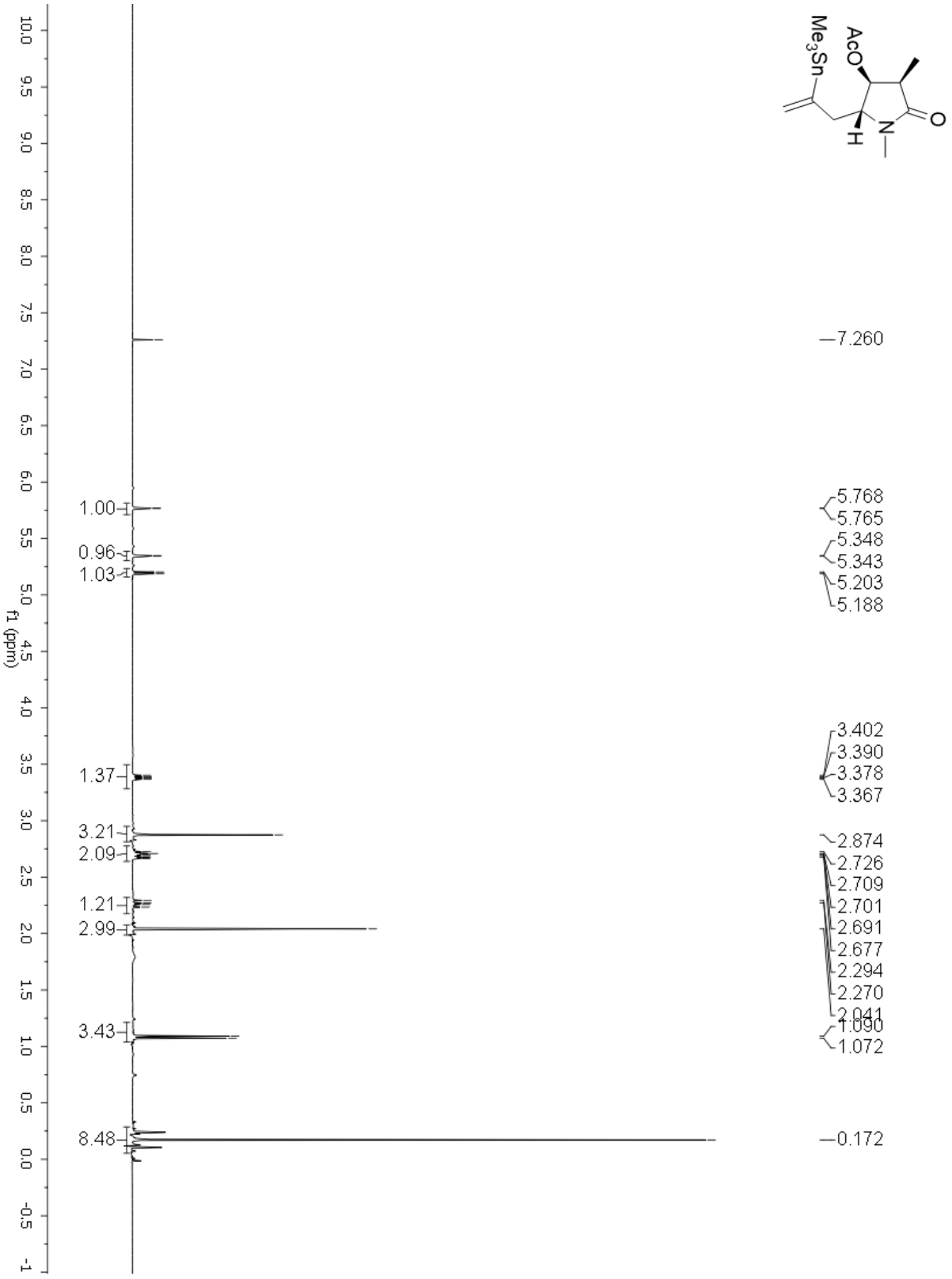

Figure 124: ^{1}H NMR of acetic acid 1,4-dimethyl-5-oxo-2-(2-trimethylstannanyl-allyl)-pyrrolidin-3-yl ester **(87)**

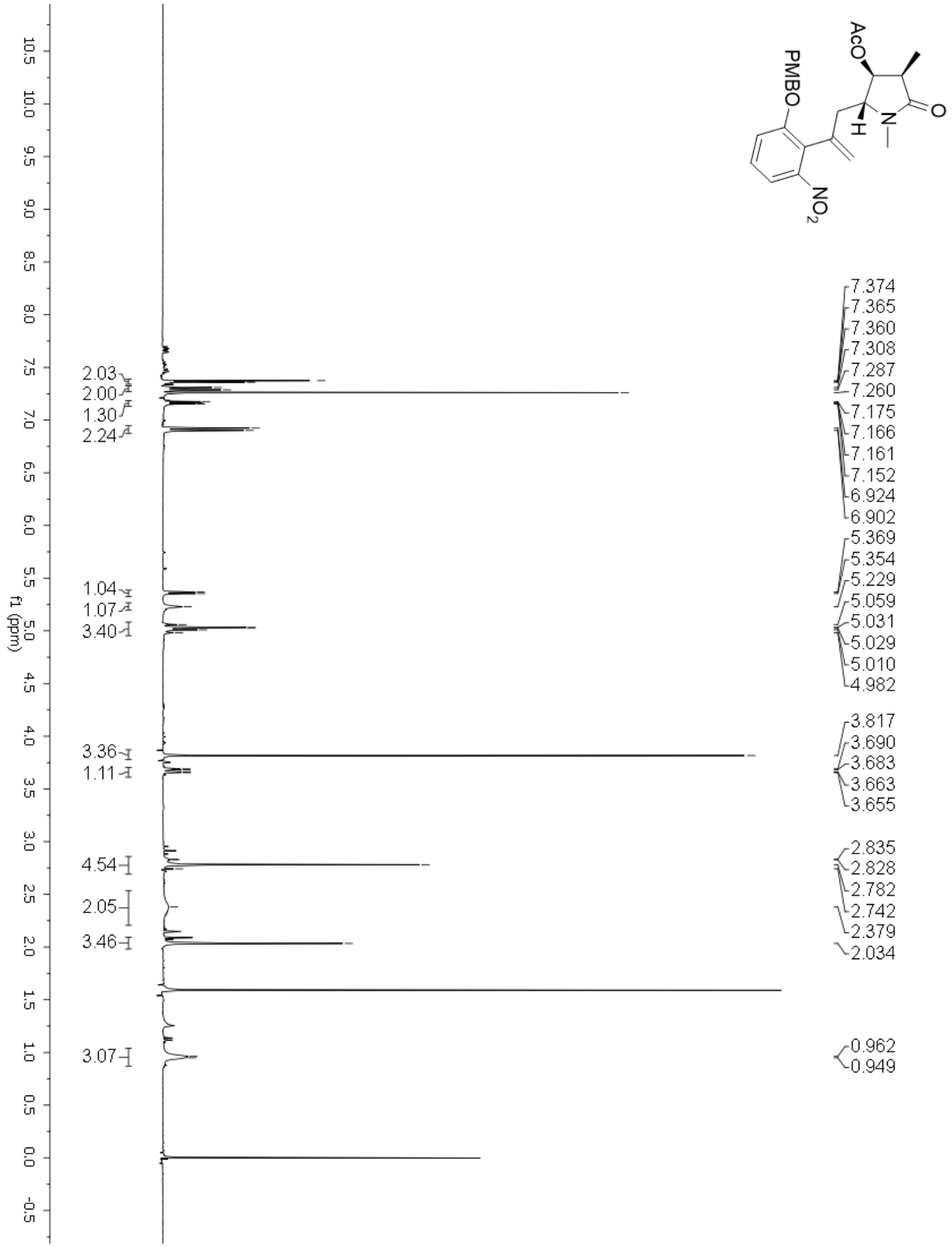

Figure 125: ^{1}H NMR of acetic acid 2-{2-[2-(4-methoxy-benzyloxy)-6-nitro-phenyl]-allyl}-1,4-dimethyl-5-oxo-pyrrolidin-3-yl ester **(80)**

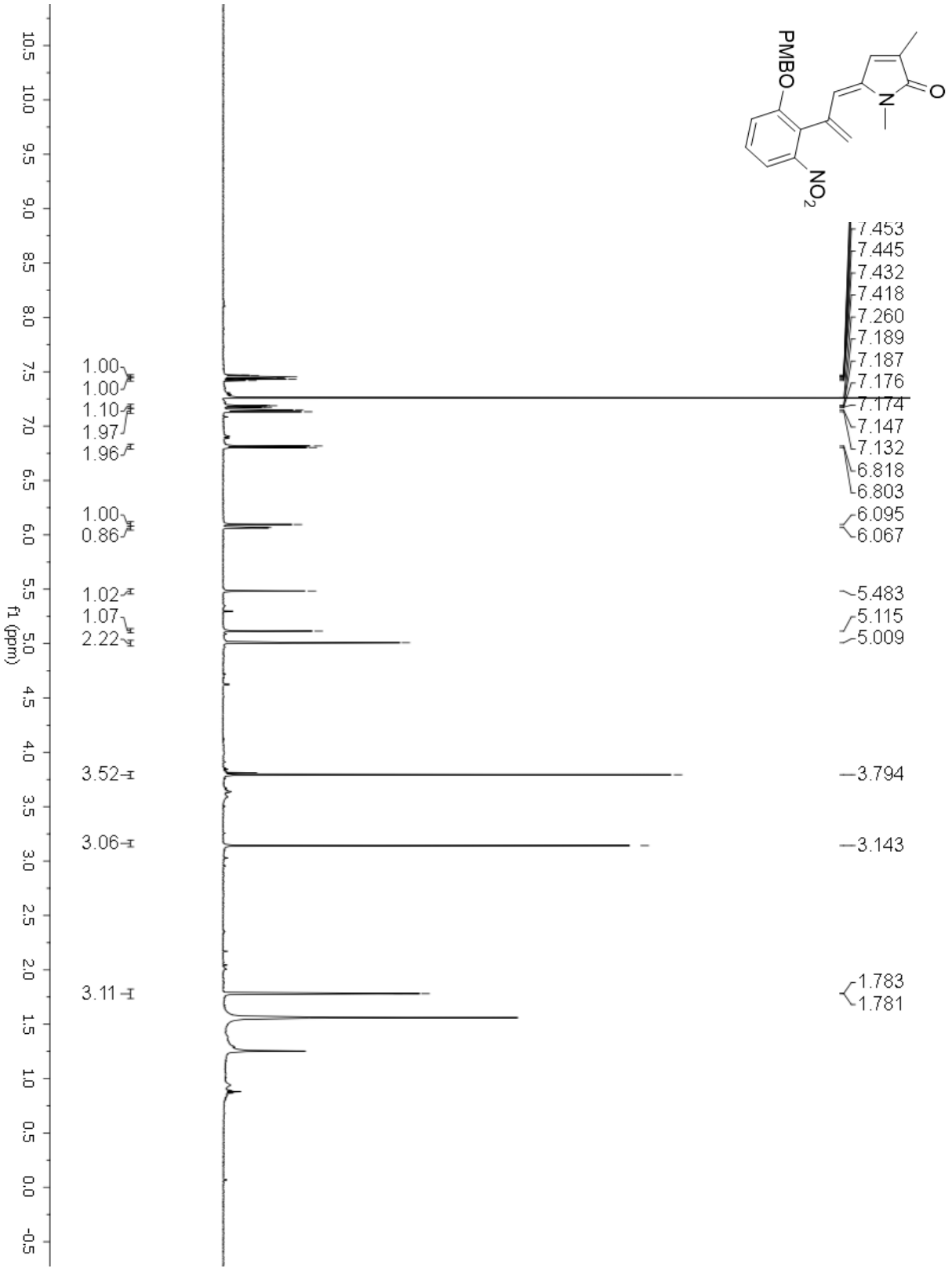

Figure 126: ^{1}H NMR of 5-{2-[2-(4-methoxy-benzyloxy)-6-nitro-phenyl]-allylidene}-1,3-dimethyl-1,5-dihydro-pyrrol-2-one **(89)**

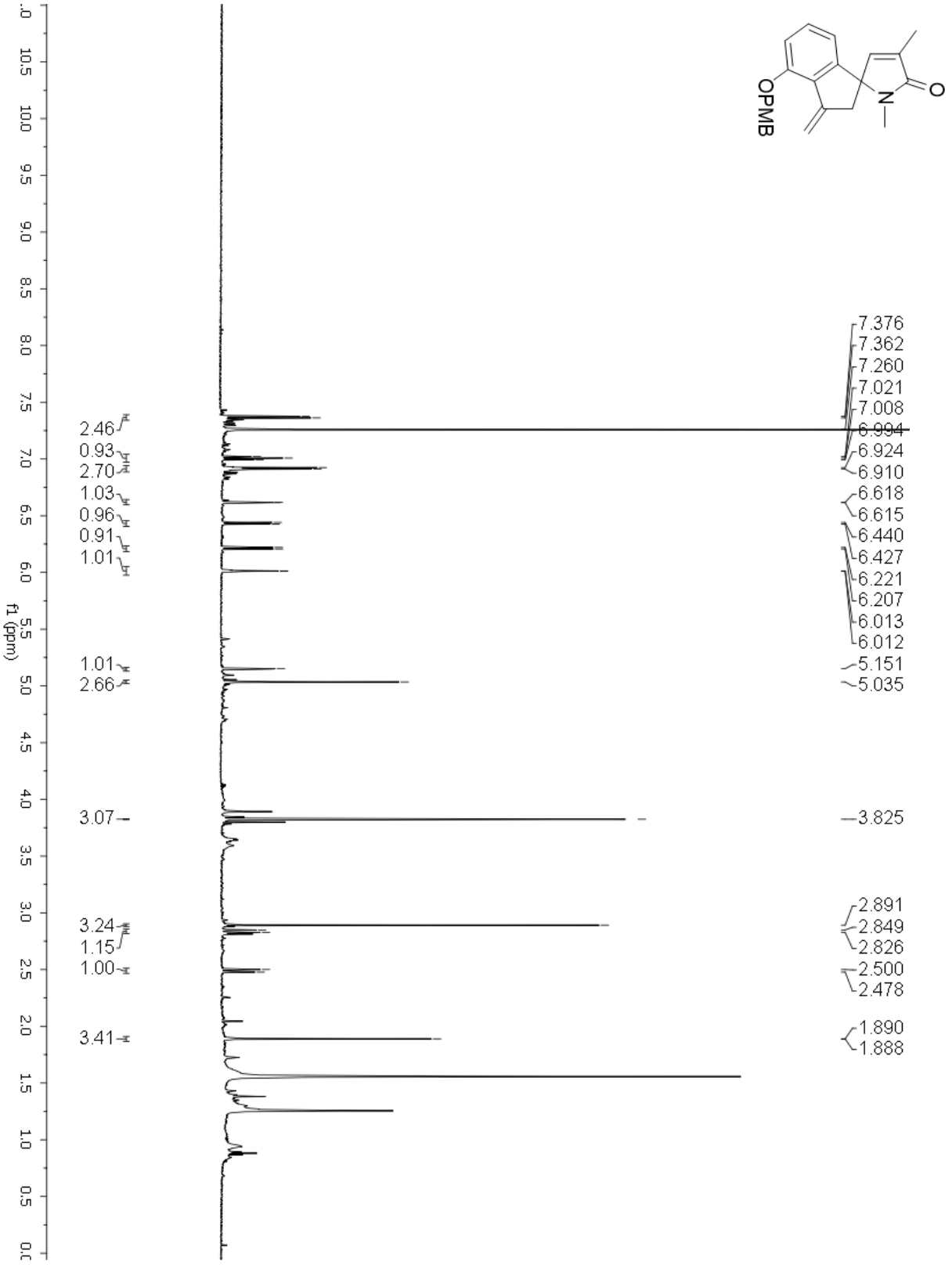

Figure 127: ^{1}H NMR of tricyclic compound **90**

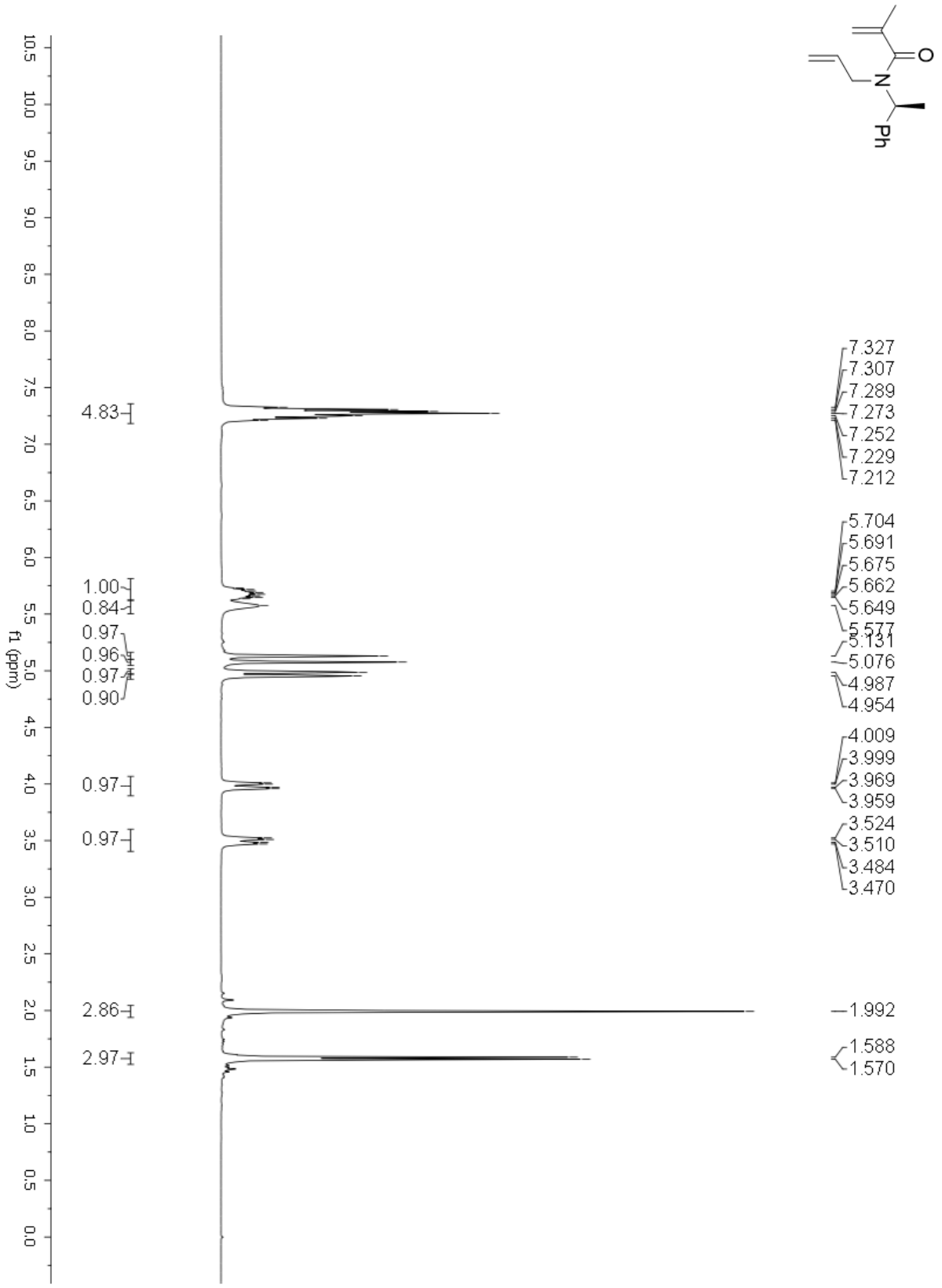

Figure 128: ^{1}H NMR of *N*-allyl-2-methyl-*N*-(1-phenyl-ethyl)-acrylamide **(92)**

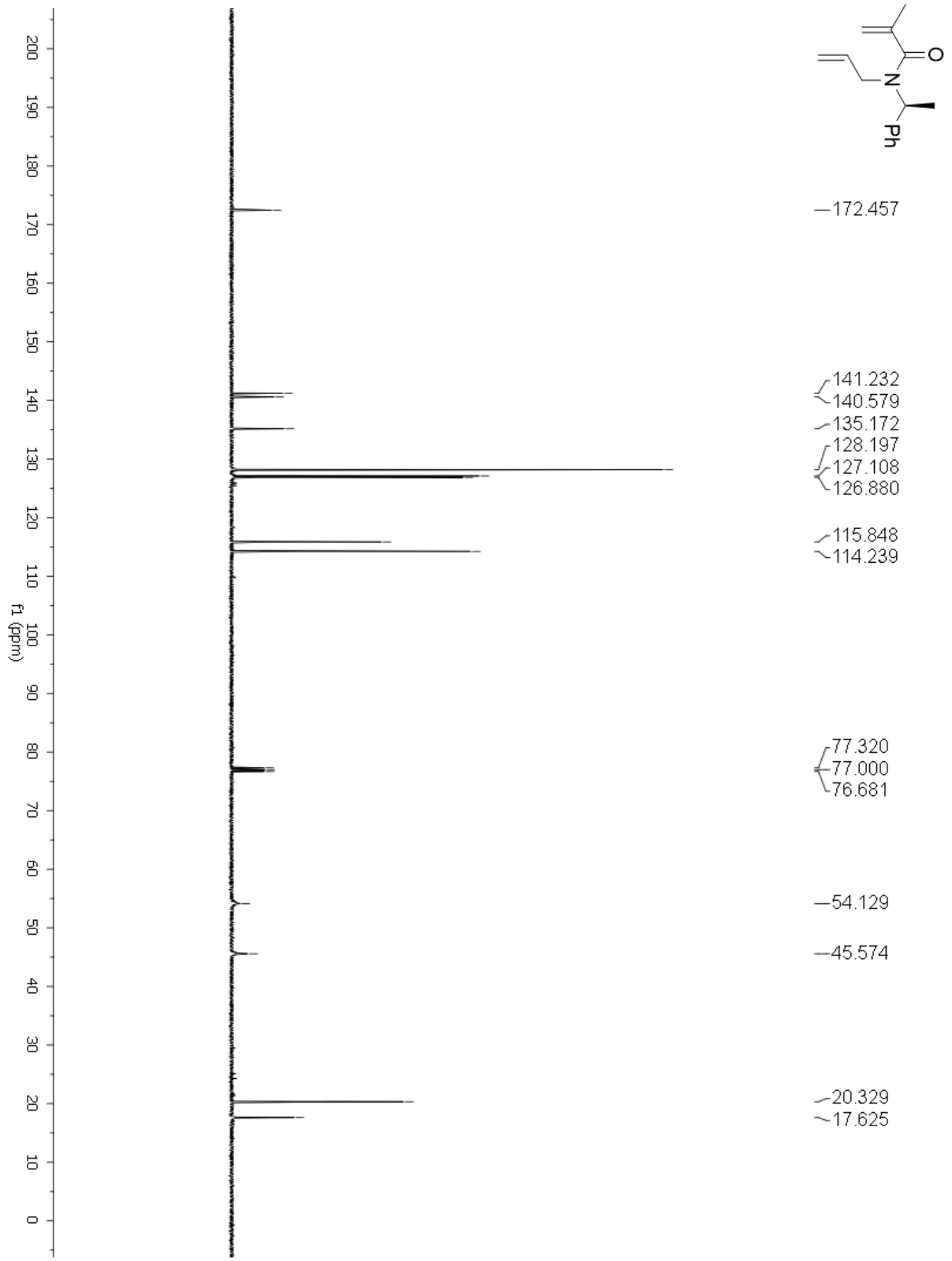

Figure 129: ^{13}C NMR of *N*-allyl-2-methyl-*N*-(1-phenyl-ethyl)-acrylamide **(92)**

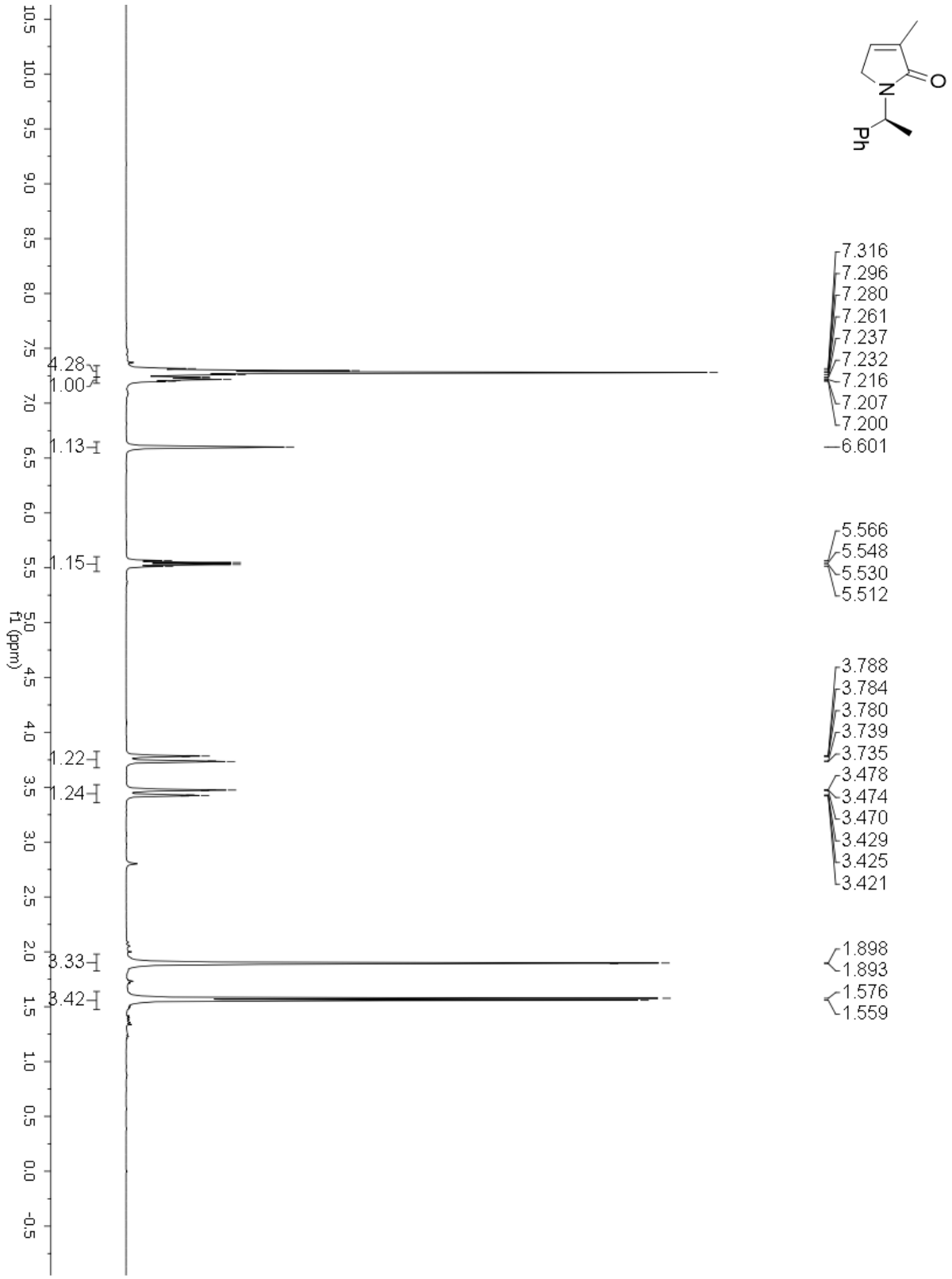

Figure 130: ^{1}H NMR of 3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one **(93)**

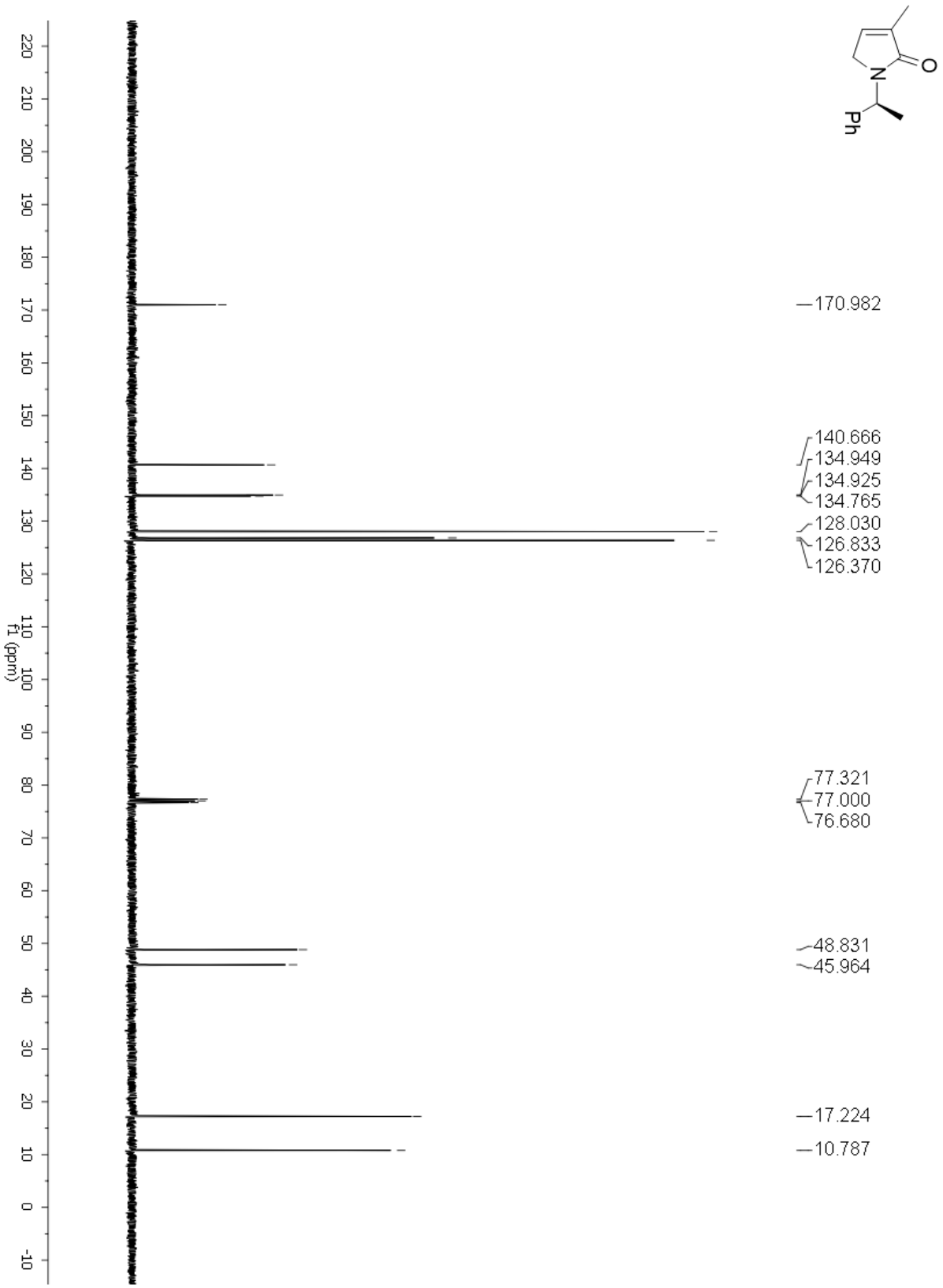

Figure 131: ^{13}C NMR of 3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one **(93)**

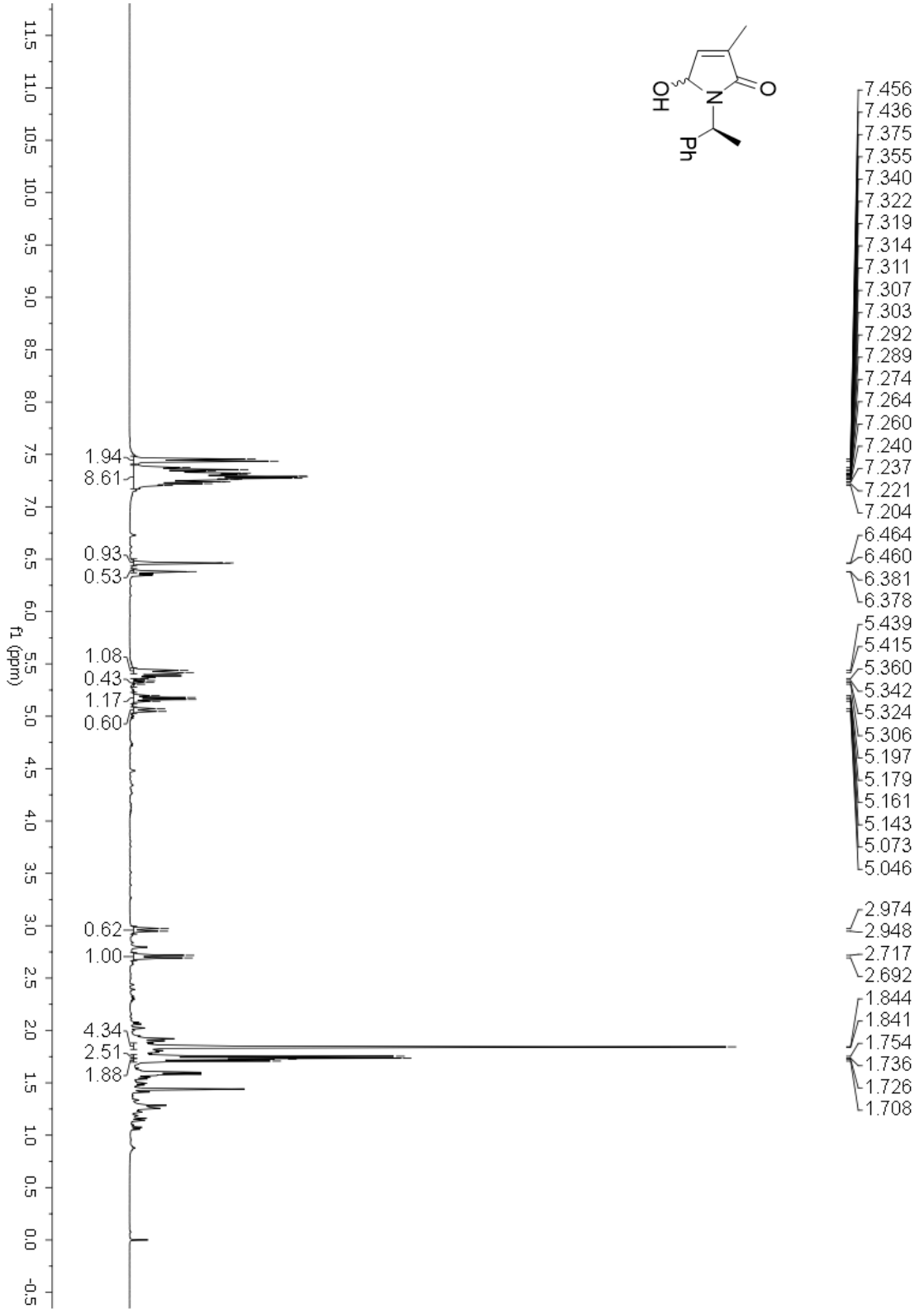

Figure 132: ^{1}H NMR of (5-hydroxy-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one **(94)**

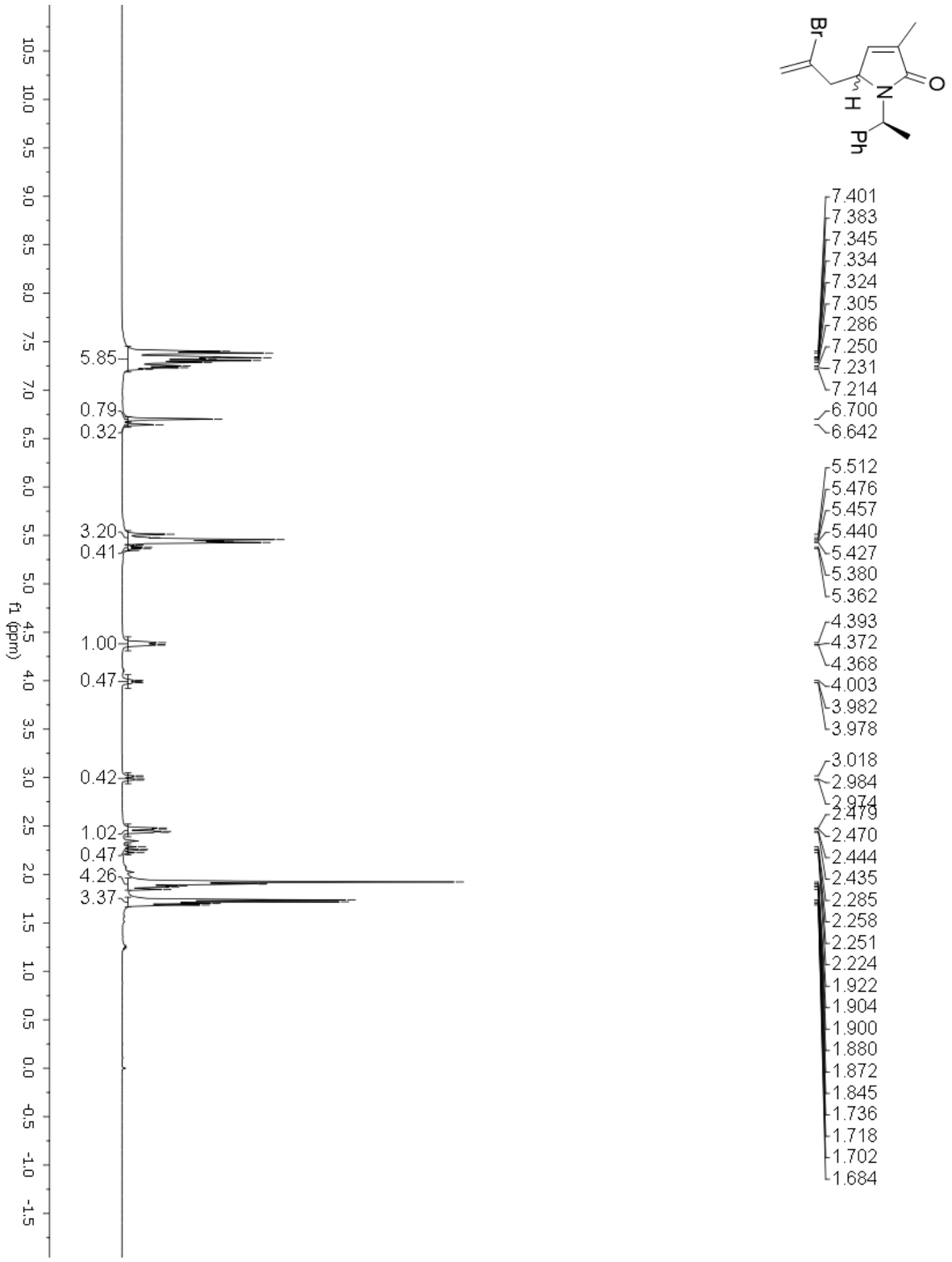

Figure 133: ^{1}H NMR of 5-(2-bromo-allyl)-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one **(95)**

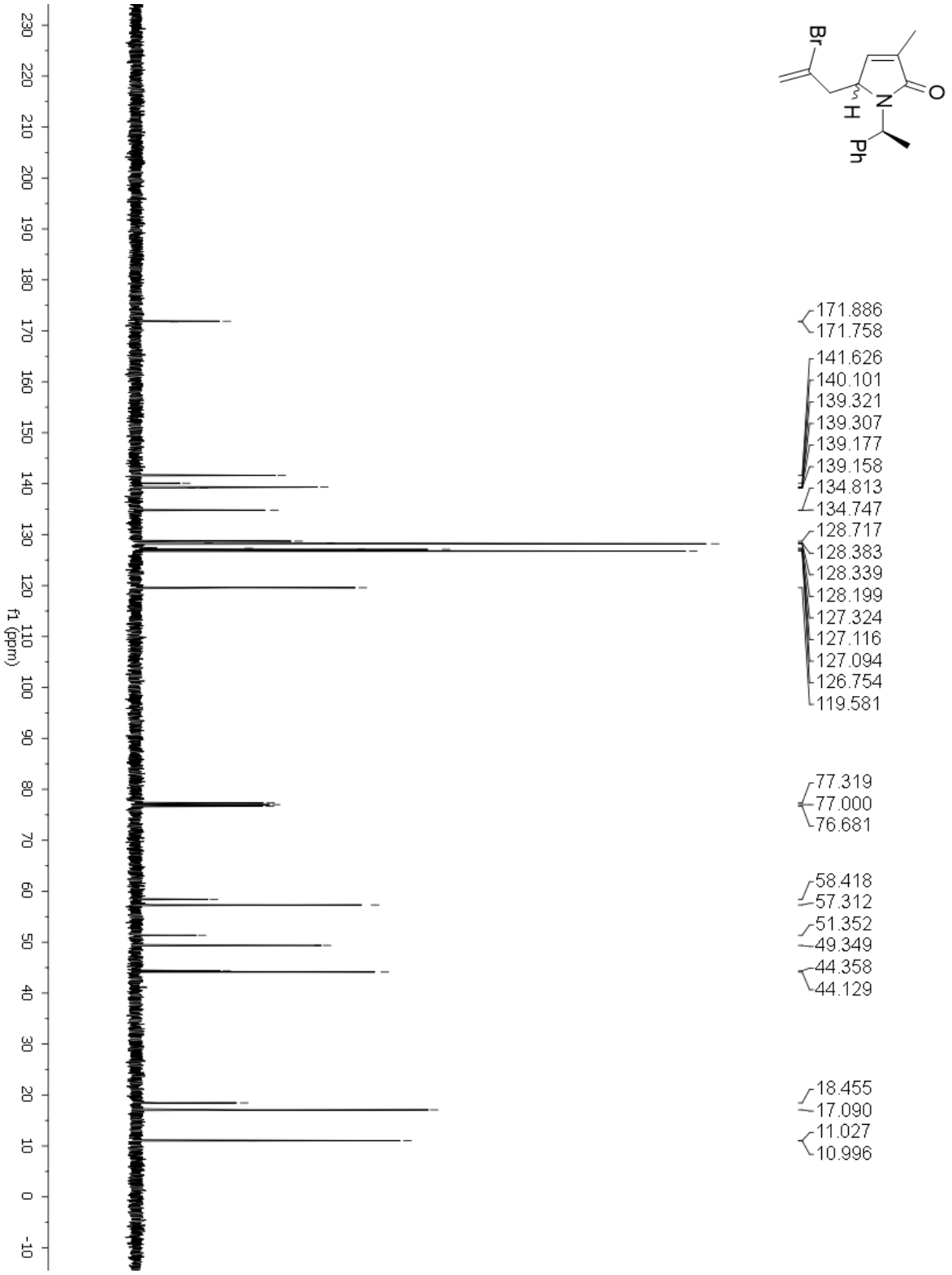

Figure 134: ^{13}C NMR of 5-(2-bromo-allyl)-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one **(95)**

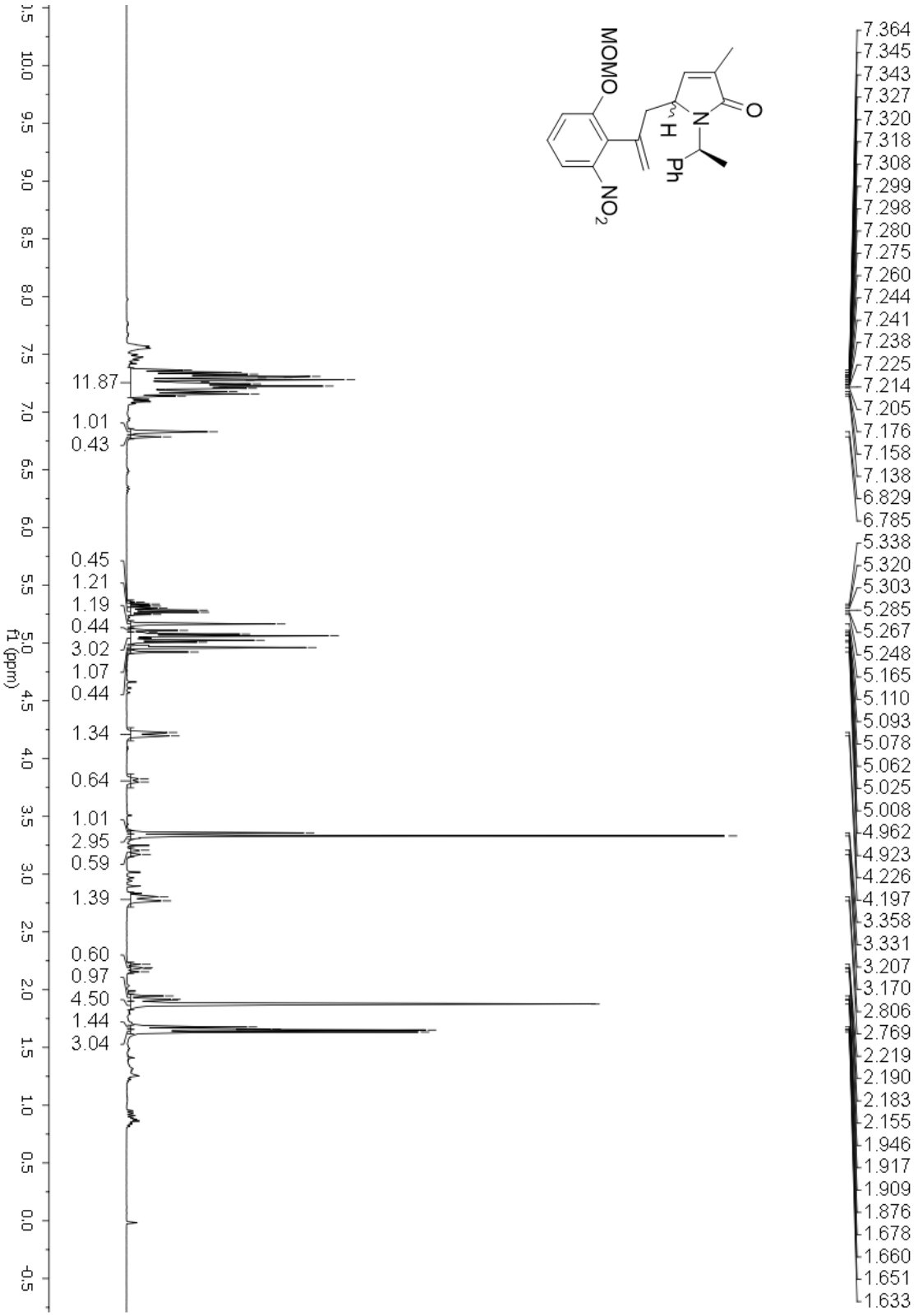

Figure 135: ^{1}H NMR (65 ^{o}C) of 5-[2-(2-methoxymethoxy-6-nitro-phenyl)-allyl]-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one **(96)**

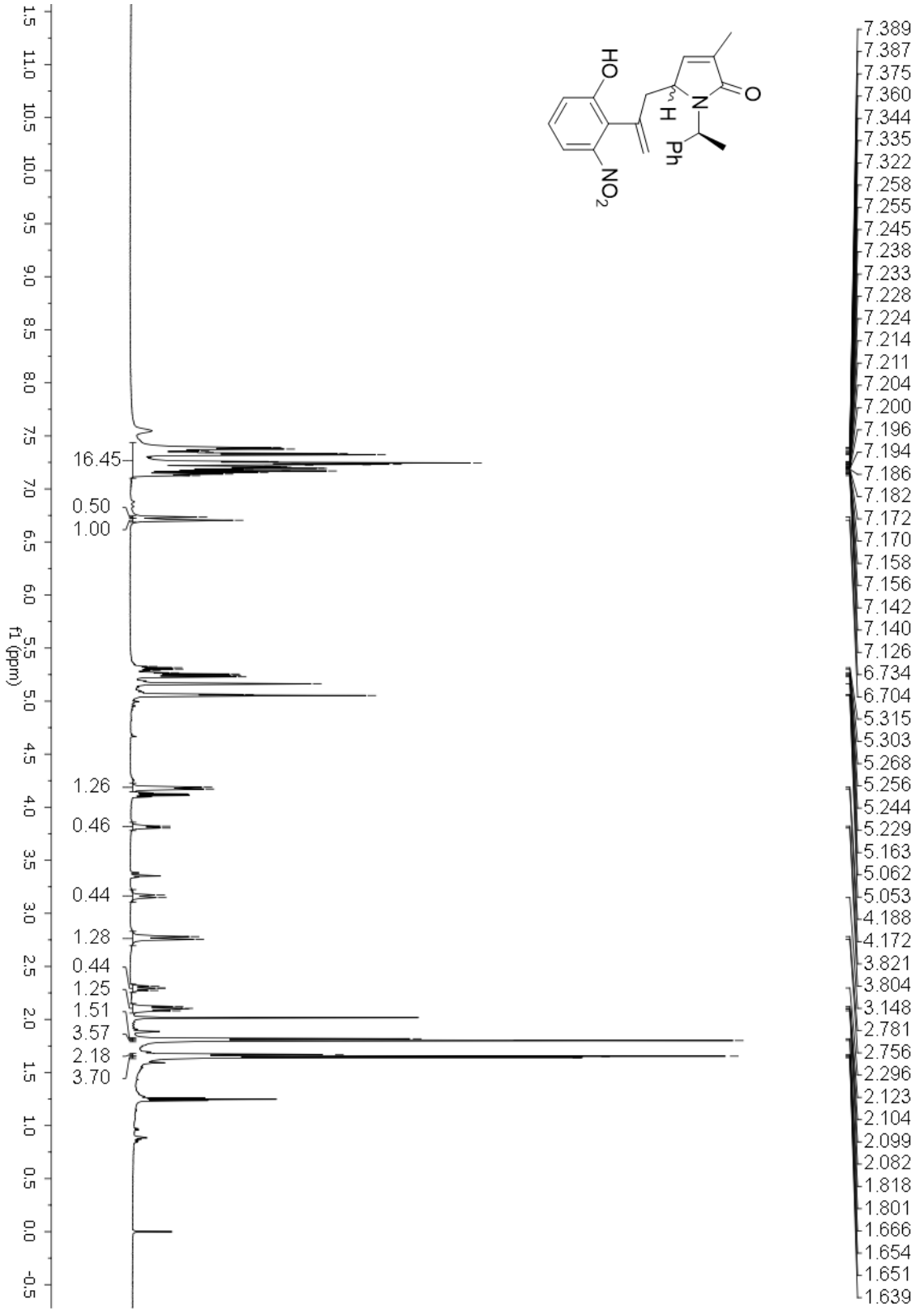

Figure 136: ^{1}H NMR (65 ºC) of 5-[2-(2-hydroxy-6-nitro-phenyl)-allyl]-3-methyl-1-(1-phenyl-ethyl)-1,5-dihydro-pyrrol-2-one **(97)**

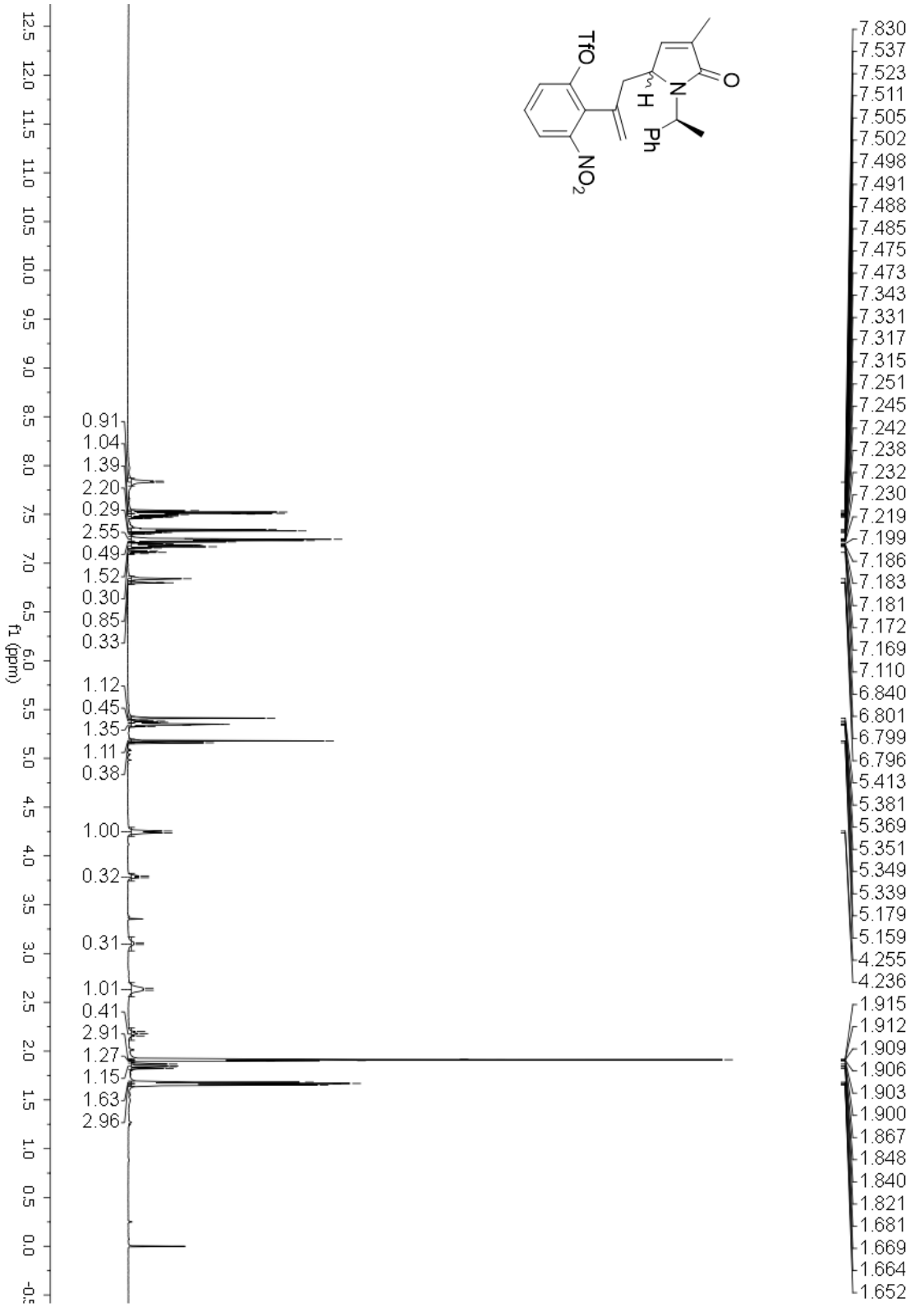

Figure 137: ^{1}H NMR (65 ºC) of trifluoro-methanesulfonic acid 2-{1-[4-methyl-5-oxo-1-(1-phenyl-ethyl)-2,5-dihydro-1H-pyrrol-2-ylmethyl]-vinyl}-3-nitro-phenyl ester **(98)**

Total synthesis of ht-13-A and ht-13-B, total synthesis of aurantioclavine, progress towards the synthesis of cycloclavine.

Yilin Zhang

Dissertation submitted to the Eberly College of Arts and Sciences at West Virginia University in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Chemistry

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APPROVAL OF THE EXAMINING COMMITTEE

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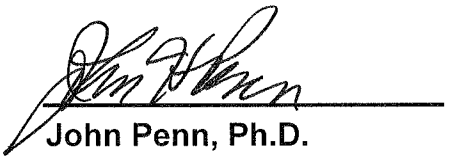

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